To: Rowland, Jess[Rowland.Jess@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]
From: Dunbar, Anwar
Sent: Fri 11/6/2015 3:21:05 PM
Subject: RE: MRID 49631701, and the other CARC DERs

Ex. 5 - Deliberative Process

Anwar Y. Dunbar, Ph.D., Pharmacologist

Risk Assessment Branch 1

The Human Health Effects Division/ The Office of Pesticide Programs

1200 Pennsylvania Ave, NW

Washington, DC 20460

"Except for in the most unique of circumstances, mastery of any cognitively complex skill or task requires roughly 10,000 hours of practice"- Malcolm Gladwell, Author of the book Outliers

From: Rowland, Jess
Sent: Friday, November 06, 2015 9:44 AM
To: Akerman, Gregory <Akerman.Gregory@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>
Subject: Re: MRID 49631701, and the other CARC DERs

G

Ex. 5 - Deliberative Process

Sent from my iPhone

On Nov 6, 2015, at 7:03 AM, Akerman, Gregory <Akerman.Gregory@epa.gov> wrote:

Ex. 5 - Deliberative Process

G

From: Akerman, Gregory
Sent: Friday, November 06, 2015 7:01 AM
Subject: RE: MRID 49631701, and the other CARC DERs

Hi Anwar,

Ex. 5 - Deliberative Process

Greg

From: Dunbar, Anwar
Sent: Thursday, November 05, 2015 4:49 PM
To: Rowland, Jess <Rowland.Jess@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>
Subject: MRID 49631701, and the other CARC DERs

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Anwar Y. Dunbar, Ph.D., Pharmacologist

Risk Assessment Branch 1

The Human Health Effects Division/ The Office of Pesticide Programs

1200 Pennsylvania Ave, NW

Washington, DC 20460

"Except for in the most unique of circumstances, mastery of any cognitively complex skill or task requires roughly 10,000 hours of practice"- Malcolm Gladwell, Author of the book Outliers

To: Akerman, Gregory[Akerman.Gregory@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]
From: Rowland, Jess
Sent: Fri 11/6/2015 2:43:42 PM
Subject: Re: MRID 49631701, and the other CARC DERs

G

Ex. 5 - Deliberative Process

Sent from my iPhone

On Nov 6, 2015, at 7:03 AM, Akerman, Gregory <Akerman.Gregory@epa.gov> wrote:

Ex. 5 - Deliberative Process

G

From: Akerman, Gregory
Sent: Friday, November 06, 2015 7:01 AM
Subject: RE: MRID 49631701, and the other CARC DERs

Hi Anwar,

Ex. 5 - Deliberative Process

Greg

From: Dunbar, Anwar
Sent: Thursday, November 05, 2015 4:49 PM
To: Rowland, Jess <Rowland.Jess@epa.gov>; Akerman, Gregory <Akerman.Gregory@epa.gov>
Subject: MRID 49631701, and the other CARC DERs

Ex. 5 - Deliberative Process

Anwar Y. Dunbar, Ph.D., Pharmacologist

Risk Assessment Branch 1

The Human Health Effects Division/ The Office of Pesticide Programs

1200 Pennsylvania Ave, NW

Washington, DC 20460

"Except for in the most unique of circumstances, mastery of any cognitively complex skill or task requires roughly 10,000 hours of practice"- Malcolm Gladwell, Author of the book Outliers

To: Rowland, Jess[Rowland.Jess@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]
From: Dunbar, Anwar
Sent: Thur 11/5/2015 9:49:19 PM
Subject: MRID 49631701, and the other CARC DERs

Ex. 5 - Deliberative Process

Anwar Y. Dunbar, Ph.D., Pharmacologist

Risk Assessment Branch 1

The Human Health Effects Division/ The Office of Pesticide Programs

1200 Pennsylvania Ave, NW

Washington, DC 20460

"Except for in the most unique of circumstances, mastery of any cognitively complex skill or task requires roughly 10,000 hours of practice"- Malcolm Gladwell, Author of the book Outliers

To: Akerman, Gregory[Akerman.Gregory@epa.gov]
Cc: Rowland, Jess[Rowland.Jess@epa.gov]
From: Wood, Charles
Sent: Wed 10/28/2015 9:12:30 PM
Subject: Re: Question regarding a histopath finding

Hi Greg,

Ex. 5 - Deliberative Process

--Charles

From: Akerman, Gregory
Sent: Wednesday, October 28, 2015 8:30 AM
To: Wood, Charles
Cc: Rowland, Jess
Subject: Question regarding a histopath finding

Good morning Charles,

Ex. 5 - Deliberative Process

Regards,

Greg

Gregory Akerman, Ph.D.

Office of Pesticide Programs, U.S. EPA

Health Effects Division
1200 Pennsylvania Avenue, NW (7509P)
Washington, DC 20460
phone: (703) 305-0116

e-mail: akerman.gregory@epa.gov

To: Akerman, Gregory[Akerman.Gregory@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]; Chen, Jonathan[Chen.Jonathan@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]
From: Rowland, Jess
Sent: Mon 9/28/2015 1:02:02 AM
Subject: Glyphosate
Glyphosate CARC FINAL 9.27.15 JR.docx

Greg et al.,

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Akerman, Gregory[Akerman.Gregory@epa.gov]
From: Rowland, Jess
Sent: Sat 9/26/2015 7:31:21 PM
Subject: RE: muta language---new version

Looks good.

I am going to send it to BUGs see if she can add anything

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Akerman, Gregory
Sent: Saturday, September 26, 2015 2:57 PM
To: Rowland, Jess
Subject: muta language---new version

Ex. 5 - Deliberative Process

To: Akerman, Gregory[Akerman.Gregory@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]
From: Perron, Monique
Sent: Tue 9/22/2015 9:12:43 PM
Subject: FW: short staff notes and noteworthy acts!!

Nice job ☺

From: Vogel, Dana
Sent: Tuesday, September 22, 2015 5:08 PM
To: OPP HED
Subject: short staff notes and noteworthy acts!!

Hi Everyone,

This week's noteworthy act award goes to … Anwar Dunbar and Greg Akerman for their hard work on the glyphosate CARC package and their well-prepared presentations to the committee. Great work Anwar and Greg!!

This week's staff notes are short. Here they are…

•□□□□□□ Communications: WPS should go out next week; OP and SU DRAs noted in the Administrator's report.

•□□□□□□ HRCOE: Martha Shimkin provided an update on the HRCOE current and future functions. A few highlights…The HRCOE is working on a schedule of HR-related activities that occur throughout the year (i.e, PARS milestones, …). Martha also meets weekly with RTP HR to get a status update on all OPP personnel actions. HRCOE is also putting together a sharepoint site where managers can go to initiate the process of personnel actions in less than 30 secs!

- □□□□□□ Need an OPP CFC rep, any takers?
- □□□□□□ SFiREG is this week
- □□□□□□ Bayer Bee tour in NC is also this week

Have a great week!

Dana

Director, Health Effects Division

Office of Pesticide Programs

USEPA

To: OPP HED[OPP_HED@epa.gov]
From: Vogel, Dana
Sent: Tue 9/22/2015 9:08:16 PM
Subject: short staff notes and noteworthy acts!!

Hi Everyone,

This week's noteworthy act award goes to … Anwar Dunbar and Greg Akerman for their hard work on the glyphosate CARC package and their well-prepared presentations to the committee. Great work Anwar and Greg!!

This week's staff notes are short. Here they are…

- Communications: WPS should go out next week; OP and SU DRAs noted in the Administrator's report.

- HRCOE: Martha Shimkin provided an update on the HRCOE current and future functions. A few highlights…The HRCOE is working on a schedule of HR-related activities that occur throughout the year (i.e, PARS milestones, …). Martha also meets weekly with RTP HR to get a status update on all OPP personnel actions. HRCOE is also putting together a sharepoint site where managers can go to initiate the process of personnel actions in less than 30 secs!

- Need an OPP CFC rep, any takers?

- SFiREG is this week

- Bayer Bee tour in NC is also this week

Have a great week!

Dana

Director, Health Effects Division

Office of Pesticide Programs

USEPA

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; OPP HED CARC[OPP_HED_CARC@epa.gov]
From: Lobdell, Danelle
Sent: Mon 9/21/2015 6:57:57 PM
Subject: RE: Glyphosate- Classification Narrative

They recently have changed the name of Hodgkin's lymphoma to Hodgkin Lymphoma… taking out the apostrophe s. See: http://www.cancer.gov/types/lymphoma

Danelle T. Lobdell, Ph.D., M.S.

Epidemiologist

National Health and Environmental Effects Research Laboratory

Environmental Public Health Division

Mail:

USEPA

MD 58A

Research Triangle Park, NC 27711

Package Delivery:

USEPA Human Studies Facility

104 Mason Farm Rd, Room 52

Chapel Hill, NC 27514-4512

Phone: 919-843-4434 Fax: 919-966-7584

From: Brunsman, Lori
Sent: Monday, September 21, 2015 2:24 PM
To: Wood, Charles; Rowland, Jess; OPP HED CARC; Lobdell, Danelle
Subject: Re: Glyphosate- Classification Narrative

I agree with Charles, although I think "Hodgkin" lymphoma should be "Hodgkin's" with an apostrophe "s".

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency
One Potomac Yard S-10934
brunsman.lori@epa.gov
703-308-2902
"When you have more than you need, build a longer table, not a higher fence."

From: Wood, Charles
Sent: Monday, September 21, 2015 1:58 PM
To: Rowland, Jess; OPP HED CARC; Lobdell, Danelle
Subject: RE: Glyphosate- Classification Narrative

Jess et al,

See edits/suggestions below in red. I borrowed several changes from others.

--Charles

From: Rowland, Jess
Sent: Monday, September 21, 2015 12:24 PM
To: OPP HED CARC; Lobdell, Danelle
Subject: Glyphosate- Classification Narrative
Importance: High

Hello CARCeers

Here is the narrative that will go into the CARC document.

I want to get this out for your comments since this “blurb” has to go into the risk assessment document which is due before the Pope get it !!!

So, u know what that means…..I need your comments by COB. It is not long…so u should make it !!

Thanks

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

From: Rowland, Jess
Location: S-10621
Importance: Normal
Subject: Accepted: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 12:00:00 PM
End Date/Time: Thur 9/10/2015 1:00:00 PM

From: Middleton, Karlyn
Location: S-10621
Importance: Normal
Subject: Accepted: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 12:00:00 PM
End Date/Time: Thur 9/10/2015 1:00:00 PM

From: Dunbar, Anwar
Location: S-10621
Importance: Normal
Subject: Accepted: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 12:00:00 PM
End Date/Time: Thur 9/10/2015 1:00:00 PM

From: Middleton, Karlyn
Location: S-10621
Importance: Normal
Subject: Declined: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 12:00:00 PM
End Date/Time: Thur 9/10/2015 1:00:00 PM

To: Akerman, Gregory[Akerman.Gregory@epa.gov]
From: Middleton, Karlyn
Sent: Mon 8/31/2015 2:32:06 PM
Subject: RE: CARC pre=meet for glyphosate

Ok.

From: Akerman, Gregory
Sent: Monday, August 31, 2015 9:56 AM
To: Middleton, Karlyn
Subject: RE: CARC pre=meet for glyphosate

Karlyn,

Sorry, I told Jess that you are chair toxsac during that time, but he said he will only be in the office on Thurs morning. He said he wants to work with Anwar on how to present the data. He said it is not necessary that you be there for that. I'm not really sure if he wants me at the meeting, but asked me to set it up.

Greg

From: Middleton, Karlyn
Sent: Monday, August 31, 2015 9:31 AM
To: Akerman, Gregory
Subject: RE: CARC pre=meet for glyphosate

Greg,

I will be chairing the dicamba ToxSAC meeting during that time (9 -11).

-----Original Appointment-----
From: Akerman, Gregory
Sent: Monday, August 31, 2015 9:16 AM
To: Rowland, Jess; Dunbar, Anwar; Middleton, Karlyn
Subject: CARC pre=meet for glyphosate
When: Thursday, September 10, 2015 9:00 AM-10:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: S-10621

Jess asked me to set up this meeting on this date and time to prep for the glyphosate CARC meeting.

From: Rowland, Jess
Location: S-10621
Importance: Normal
Subject: Accepted: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 1:00:00 PM
End Date/Time: Thur 9/10/2015 2:00:00 PM

From: Middleton, Karlyn
Location: JR's office
Importance: Normal
Subject: Accepted: CARC pre-meet for glyphosate
Start Date/Time: Thur 5/14/2015 3:00:00 PM
End Date/Time: Thur 5/14/2015 4:00:00 PM

From: Rowland, Jess
Location: JR's office
Importance: Normal
Subject: Accepted: CARC pre-meet for glyphosate
Start Date/Time: Thur 5/14/2015 3:00:00 PM
End Date/Time: Thur 5/14/2015 4:00:00 PM

To: Akerman, Gregory[Akerman.Gregory@epa.gov]
From: Rowland, Jess
Sent: Tue 5/12/2015 1:49:01 PM
Subject: Couple

If Amy available Thursday....book her
You and I meet with karlyn on Glyphosate carc...tomorrow or Thursday
Thanks
Sent from my Windows Phone

From: Blankinship, Amy
Location: S-10621
Importance: Normal
Subject: Accepted: WOE work
Start Date/Time: Mon 3/30/2015 5:00:00 PM
End Date/Time: Mon 3/30/2015 7:00:00 PM

I have a meeting with Monsanto at 2:30 regarding glyphosate, so I will have to leave before 3 pm

To: Shah, Pv[Shah.Pv@epa.gov]
From: Akerman, Gregory
Sent: Wed 4/13/2016 8:55:33 PM
Subject: RE: Glyphosate cancer for monograph 4 10 16 ga

Ex. 5 - Deliberative Process

From: Shah, Pv
Sent: Wednesday, April 13, 2016 4:21 PM
To: Akerman, Gregory <Akerman.Gregory@epa.gov>
Subject: RE: Glyphosate cancer for monograph 4 10 16 ga

Ex. 5 - Deliberative Process

PV

P. V. Shah, Ph.D
Chief, Chemistry, Inerts and Toxicology Assessment Branch (CITAB)
Registration Division
Office of Pesticides Programs, US EPA
1200 Pennsylvania Ave., NW
Washington, DC 20460 (USA)
Phone: 703-308-1846
Fax: 703-605-0781
Shah.Pv@epa.gov

For FED EX and UPS Deliveries: One Potomac Yard (South Building), 2777 Crystal Drive (Room S-7751), Arlington, VA 22202

From: Akerman, Gregory
Sent: Wednesday, April 13, 2016 4:11 PM

To: Shah, Pv <Shah.Pv@epa.gov>
Subject: Glyphosate cancer for monograph 4 10 16 ga

Ex. 5 - Deliberative Process

Greg

To: Smith, Charles[Smith.Charles@epa.gov]
From: Akerman, Gregory
Sent: Wed 11/18/2015 1:25:35 PM
Subject: RE: a process question

Sorry, Forgot to include that: MRID 00130406

From: Smith, Charles
Sent: Wednesday, November 18, 2015 8:25 AM
To: Akerman, Gregory <Akerman.Gregory@epa.gov>
Subject: RE: a process question

I can but I need the MRID.

Charles " Billy" Smith

Branch Chief RAB1

Health Effects Division

Office of Pesticide Programs

703-305-0291

From: Akerman, Gregory
Sent: Wednesday, November 18, 2015 8:24 AM
To: Smith, Charles <Smith.Charles@epa.gov>
Subject: FW: a process question

Hi Billy,

We updated a cancer DERs for glyphosate when the chemical went to CARC. The existing 2-page DER was old and JR asked that it be updated to provide more detail. There was no bean for this action. I'm now trying purple folder this DER. Rick W. suggested that I ask you to create a subbean off an existing glyphosate action so that I can out process this DER. Will you create a subbean for this?

Thanks,

Greg

From: Whiting, Rick
Sent: Wednesday, November 18, 2015 8:03 AM
To: Akerman, Gregory <Akerman.Gregory@epa.gov>
Subject: Re: a process question

Greg,

Interesting question. You could send it to Billy Smith since his branch is handling Glyphosate. As for a bean, Billy might be able to create a subbean off an existing Glyphosate action.

Rick J Whiting

Science Information Management Branch (SIMB)
Health Effects Division (Mail Code 7509P)
Office of Pesticide Programs, US EPA

whiting.rick@epa.gov
(703) 305-5473

From: Akerman, Gregory
Sent: Wednesday, November 18, 2015 7:56 AM
To: Whiting, Rick
Subject: a process question

Hi Rick,

I have a stupid question for you. I have a revised DER (updated from one of those old 2 page DERs to a full-size DER) for glyphosate that I need to out process. There was no Bean for this action. Jess decided during the CARC review that the level of information in the existing DER was insufficient. How do I purple folder this? I can draft a memo, but I don't know who to send it to since there is no bean.

Thanks,

Greg

To: Nguyen, Khue[Nguyen.Khue@epa.gov]
From: Akerman, Gregory
Sent: Mon 9/14/2015 6:41:41 PM
Subject: request for glyphosate beans

HI Khue,

Ex. 5 - Deliberative Process

Regards,

Greg

Gregory Akerman, Ph.D.

Office of Pesticide Programs, U.S. EPA

Health Effects Division
1200 Pennsylvania Avenue, NW (7509P)
Washington, DC 20460
phone: (703) 305-0116

e-mail: akerman.gregory@epa.gov

To: Schlosser, Christopher[Schlosser.Christopher@epa.gov]
From: Akerman, Gregory
Sent: Thur 9/10/2015 11:47:38 AM
Subject: one more to upload please
1983 mouse MRID 00130406 Monsanto.doc

Chris,

Will you please upload this DERs to the CARC dbase for glyphosate--- under the DERs and support docs section.

Thanks!

Greg

DATA EVALUATION RECORD

GLYPHOSATE

STUDY TYPE: CARCINOGENICITY – MOUSE

OCSPP 870.4200b

ACC. NO. 251007014

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
Knoxville, Tennessee 37922

Task Order No. 6-148

Primary Reviewer: H.T. Borges, Ph.D., MT(ASCP), D.A.B.T. (1994-2014)	Signature: Date:	H.T. Borges 08/31/2015
Secondary Reviewers: Thomas C. Marshall, Ph.D., D.A.B.T.	Signature: Date:	Thomas C. Marshall 08/31/2015
Robert H. Ross, M.S., Program Manager	Signature: Date:	Robert H. Ross 08/31/2015
Quality Assurance: Angela M. Edmonds, B.S.	Signature: Date:	Angela M. Edm 08/31/2015

Disclaimer
This review may have been altered subsequent to the contractor's signatures above.

Summitec Corp. for the U.S. Environmental Protection Agency under Contract No.EP-W-11-014

EPA Reviewer: Ray Kent **Signature**: ______________
Risk Assessment Branch 1, Health Effects Division (7509P) **Date:** ______________
EPA Secondary Reviewer: J. Rowland **Signature**: ______________
Health Effects Division (7509P) **Date:** ______________
Template version 03/12

TXR#: 0057297

DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity - mice, feeding study
OCSPP 870.4200b [§83-2b]; OECD 451.

PC CODE: 417300 **DP BARCODE**: NA

TEST MATERIAL (PURITY): Glyphosate (ROUNDUP® Technical), 99.7% a.i.

SYNONYMS: N-(Phosphonomethyl)glycine

CITATION:
Knezevich, A.; Hogan, G. (1983) A Chronic Feeding Study of Glyphosate (Roundup Technical) in Mice: Project No. 77-2061: BDN-77- 420. Final rept. (Unpublished study received Aug 17, 1983 under 524-308; prepared by Bio/dynamics, Inc., submitted by Monsanto Co., Washington, DC; CDL:251007-A; 251008; 251009; 251010; 251011; 251012; 251013; 251014). MRID 00130406

SPONSOR: Monsanto Company, St. Louis, MO 63166 (Attn: Dr. Richard Dirks)

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID 00130406), glyphosate (ROUNDUP® Technical, 99.7% a.i.) was administered to groups of 50 male and 50 female CD-1 mice/sex/dose in the diet at dose levels of 0, 1000, 5000, or 30,000 ppm (approximately equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Cage-side and detailed clinical observations were done. Body weight and food intake were monitored throughout the study. Water consumption was measured during months 12 and 24. Erythrocyte, as well as total white cell counts and differentials, were done at months 12, 18, and 24. Tissues and organs were collected from all mice whether dying during the study or at terminal sacrifice. Microscopic analyses were done on all collected tissues.

No treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weight of high-dose males was significantly decreased 9% while the absolute liver weight of high-dose males was significantly decreased 16%; however, no significant treatment-related effects were found on the liver to body weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17%. Neither were statistically significant, and no microscopic histological correlates were found. The incidences of centrilobular hepatocyte hypertrophy were slightly, but not significantly increased in high-dose

male mice. Centrilobular hepatocyte necrosis was significantly increased in high-dose males (10/50** (20%) vs control 2/49 (4%), $p \leq 0.01$). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice; however, proximal tubular epithelial basophilia was significantly increased in high-dose females (9/50** (18%) vs control 0/50 (0%), $p \leq 0.01$). No other microscopic treatment-related effects were found.

Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 5000 ppm (approximately 835 mg/kg bw/day for males and 968 mg/kg bw/day for females).

There were a number of tumor types observed in the cancer study, however renal tubular adenomas of the kidney in male mice were the only neoplastic lesion considered to be potentially treatment related.

This carcinogenicity study in mice is **Acceptable / Non-guideline** and does not satisfy guideline requirements for a carcinogenicity study [OCSPP 870.4200; OECD 451] in mice. However, the study was conducted before establishment of OCSPP 870.4200 recommendations.

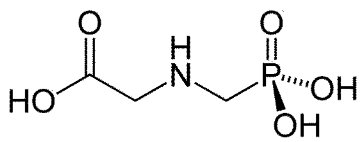
COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were not provided. The study was conducted prior to establishment of US EPA GLP regulations and before US EPA Guideline recommendations contained in OCSPP 870.4200.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Glyphosate (ROUNDUP® Technical)

Description: Fine, white clumped powder
Lot/batch #: Lot Nos. NB 1782608 and NB 1782610
Purity: 99.7% a.i.
Compound stability: Not reported but was determined by study sponsor
CAS # of TGAI: 1071-83-6
Structure:



2. Vehicle: Purina Rodent Laboratory Chow #5001

3 Test animals:

Species: Mice
Strain: CD-1, COBS (ICR derived)
Age/weight at study initiation: 40 days / Males 16 – 28 g, females 15 – 24 g
Source: Charles River Breeding Laboratories, Inc., Portage, MI 19081
Housing: Individually in stainless steel wire mesh cages during study
Diet: Purina Rodent Laboratory Chow #5001, *ad libitum*
Water: Elizabethtown Water Co. water, *ad libitum*
Environmental conditions: **Temperature:** 18.3 – 23.3°C
Humidity: 15 - 75%
Air changes: Not reported
Photoperiod: 12 hours light/dark
Acclimation period: 11 days

B. STUDY DESIGN:

1. **In-life dates:** Start: March 31, 1980 End: March, 7, 11, or 14, 1982

2. **Animal assignment/dose levels:** Animals were assigned to the groups shown in Table 1 based on body weight.

Table 1: Study design

Group	Conc. in diet (ppm)	Approximate average dose Males / Females (mg/kg bw/day) [a]	Range of doses Male / Females (mg/kg bw/day)	Main study (24 months)		Hematology studies at 12, 18, and 24 months	
				Males	Females	Males	Females
Control	0	0 / 0	0 / 0	50	50	10	10
Low	1000	161 / 195	110.9-249.9 / 128.9-287.8	50	50	10	10
Mid	5000	835 / 968	519.3-1264.2 / 689.7-1321.5	50	50	10	10
High	30,000	4945 / 6069	3465.0-7219.8 / 4232.4-9858.6	50	50	10	10

Data from page 34 of Project No. 77-2061
[a] Provided with the "Best Document Available" the approximate average dose was calculated by the reviewer from legible data on pages 100 – 112 of study report. Of a total possible 58 results collected weekly or bi-weekly, N was 57, 55, and 54 for males and 58, 57, and 57 for females in the low-, mid-, and high doses, respectively.

3. **<u>Dose selection</u>:** A dose selection rationale was not located in the study report, but the high dose for both males and females exceeds the limit dose

4. **<u>Diet preparation and analysis</u>:** Diets were prepared weekly by mixing appropriate amounts of test substance with Purina Rodent Laboratory Chow #5001 to generate diets containing 1000, 5000, and 30,000 ppm. Diet storage was not reported. Homogeneity of the test material in the diet was determined from the first diet preparation (March 4, 1980) from triplicate samples collected from the top, middle, and bottom of each preparation by the study sponsor. Diet samples from each preparation were collected weekly for the first month of the study and monthly thereafter for concentration. These were sent to the study sponsor for analyses to determine the stability and concentration of the test material in the preparations (pages 422 – 444 of study report). The performing laboratory also did stability and concentration analyses on all samples (pages 45 – 475 of study report). Both the study sponsor and performing laboratory analyzed diet samples by HPLC collected on Weeks 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 60, 72, 84, 96, and 102.

<u>Results:</u>
Homogeneity analysis: The coefficient of variation for the 1000, 5000, and 30,000 diets analyzed by the study sponsor from samples collected from the top, middle, and bottom of the mixing chamber ranged from 3.88 – 5.48%, indicating the diets were properly mixed.

Stability analysis: The test material was shown to be stable for the 7-day use of the diets by both the study sponsor and the performing laboratory. Diets analyzed on Day 7 by the study sponsor were 97.2%, 98.8%, and 101.3% of the Day 1 result while diets analyzed by the performing laboratory were 97.9%, 99.0%, and 103.1% of the Day 1 result for the 1000, 5000, and 30,000 ppm diets, respectively, indicating that test material stability was acceptable.

Concentration analysis: Average diet concentration analyses done by the study sponsor were 93.2%, 95.1%, and 96.8% of nominal while those done by the performing laboratory were 92.5% 94.6%, and 96.5% of nominal for the 1000, 5000, and 30,000 ppm diets, respectively, indicating that test material concentration was acceptable..

5. **<u>Statistics</u>:** Body weight and body weight gain, food consumption, feed efficiency, water consumption, hematology parameters, terminal organ and body weights, and organ to body weight and organ to brain weight were analyzed statistically. No reference was made to the calculation of incidence data. For the above parameters, statistical evaluations of equality of means was made by the appropriate one way analysis of variance technique, followed by a multiple comparison procedure if needed. First, Bartlett's test was done to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not, nonparametric procedures were used. The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from the control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from the control.

A statistical significance test for trend was also done. In parametric analyses, standard regression techniques with a test for trend and lack of fit were used. In the nonparametric analyses, Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1%, two-sided risk level prior to analysis of parametric or nonparametric data. All other statistical tests were conducted at the 5% and 1%, two-sided risk levels.

The reviewer considers the methods used for continuous data appropriate.

C. METHODS:

1. Observations:

1a. Cage-side observations: Animals were inspected twice daily for signs of toxicity and mortality.

1b. Detailed clinical examinations: Detailed clinical examinations were done weekly throughout the study to determine signs of local or systemic toxicity, pharmacological effects and for palpable tissue masses.

2. Body weight: The mice were weighed twice before the start of the study, weekly through 14 weeks of treatment, every other week thereafter, and at terminal sacrifice (fasted).

3. Food consumption and compound intake: Food consumption for each mouse was determined once before the start of the study, weekly through the first 14 weeks of treatment, and every other week through the remainder of the study. Food efficiency ((g/interval divided by the current body weight) × 100) and compound intake (mg/kg bwt/day) were calculated as time-weighted averages from the consumption and body weight gain data. Compound consumption was provided as a range in the study report, however, the reviewer calculated an approximate average compound consumption from data provided in the study report.

4. Water consumption: Water consumption was measured from 10 mice/sex/dose at Month 12 over a 3-day period. Because of the high mortality across all dose groups during Month 24, water consumption was measured on 12 mice/sex/dose for a 3-day period, followed by a 2-day period.

5. Ophthalmoscopic examination: Ophthalmoscopic examinations were not done. (Ophthalmoscopic examinations are not required by OCSPP 870.4200.)

6. Hematology and clinical chemistry: Blood was collected by retrobulbar puncture under light ether anesthesia from 10 mice/sex/dose from fasted animals during Months 12 and 18. At Month 24, blood was collected from 12 male mice/group and from all surviving female mice/group. In the following table the checked (X) hematological parameters were examined. As much as possible, the same mice were used for each blood collection. Clinical chemistry analyses were not done and aren’t required by OCSPP 870.4200.

Hematology:

X	Hematocrit (HCT)	X	Leukocyte differential count*
X	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)		Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
	Blood clotting measurements	X	Erythrocyte morphology
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Minimum required for carcinogenicity studies (Control and HDT unless effects were observed) based on Guideline OCSPP 870.4200 and OECD 451

6. **Urinalysis:** Urinalysis was not done or required by OCSPP 870.4200.

7. **Sacrifice and pathology:** All animals that died prior to, and those sacrificed on schedule by exsanguination under ether anesthesia were subjected to gross pathological examinations and the checked (X) tissues were collected for histological examination. Only tissues collected at terminal sacrifice were weighed (XX organs). All collected tissues of mice dying before scheduled sacrifice (if available) and at terminal sacrifice were examined microscopically for neoplastic and non-neoplastic effects. The following tissues were examined microscopically on 10 mice/sex/group: spinal cord sections (cervical and thoraco-lumbar), and sections through the head (nasal cavity, paranasal sinuses, tongue, oral cavity, nasopharynx, and middle ear).

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (retina, optic nerve)*
X	Jejunum*	X	Thymus	**X**	**GLANDULAR**
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	**X**	**UROGENITAL**		Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroids*
	Rectum*	X	Urinary bladder*	X	Thyroids*
XX	Liver*+	XX	Testes*+	**X**	**OTHER**
X	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*		Seminal vesicle*	X	Skin*
X	**RESPIRATORY**	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	X	Uterus*+	X	Head
X	Lung*++	X	Mammary gland*		
X	Nose*				
X	Pharynx*				
	Larynx*				

* Required for carcinogenicity studies based on Guideline OCSPP 870.4200.
\+ Organ weight required in carcinogenicity studies.
++ Organ weight required if inhalation route

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** While incidences of yellow staining of the anogenital area, scabbing on the ears, alopecia, excessive lacrimation, displacement of the pupils, and ocular opacities were observe in all groups of male and female mice, none were dose-related and all occurred at low incidences.

2. **Mortality:** As shown in Table 2, survival of male and female mice was not affected by treatment with glyphosate. The mortality incidence demonstrated no dose- or test material-related adverse effects. Survival at 18 months was greater than OCSPP 870.4200 Guideline recommendation of 25%.

Table 2. Percent survival of male and female mice treated up to 24 months with glyphosate

Month	Dietary dose (ppm)			
	0	1000	5000	30,000
		Males		
12	82	82	86	92
18	76	62	72	78
24	40	32	34	52
		Females		
12	94	92	98	90
18	70	68	84	74
24	40	24	54	46

Data extracted from pages 39 and 44 of Project No. 77-2061 (MRID 00130406)

B. BODY WEIGHT:

The body weight of high-dose male mice was decreased significantly at most weighing intervals throughout the study. As shown in Table 3, the body weight of high-dose male mice was decreased 11% by Week 102 relative to control mice, and the overall body weight gain was decreased by 26%. The body weight gain of mid-dose male mice was decreased 13% by study end relative to control mice, but the body weight was not statistically significant. Although sporadic statistically significant differences from control mice were found in body weight of all groups of treated female mice, the effects were not dose- or treatment-related

Table 3: Mean bodyweight (BW, g) and bodyweight gain (BWG, g) of CD-1 mice treated with glyphosate up to 102 weeks

Treatment period	Dose (ppm)				Dose (ppm)			
	0	1000	5000	30,000	0	1000	5000	30,000
	Males				Females			
BW week 0	22.6^{50}	22.8^{50}	22.5^{50}	22.5^{50}	20.3^{50}	20.5^{50}	19.9^{50}	19.6^{49}
BW week 13	34.8^{48}	$33.3{*}^{50}$	35.1^{50}	$33.2{**}^{50}$	28.9^{50}	29.5^{49}	29.3^{50}	28.8^{50}
BW week 24	35.6^{47}	34.7^{49}	35.3^{48}	35.5^{50}	31.0^{50}	31.3^{48}	30.7^{50}	30.9^{48}
BW week 52	36.4^{41}	35.0^{41}	36.1^{43}	$33.8{**}^{47}$	32.3^{48}	33.1^{46}	$30.0{**}^{49}$	32.1^{45}
BW week 76	38.8^{40}	37.1^{33}	38.5^{39}	37.7^{39}	32.6^{36}	34.2^{37}	32.9^{42}	32.1^{37}

BW week 102	37.7[18]	37.9[14]	35.7[15]	33.6**[24]	35.1[28 a]	37.6[19 a]	NL [a]	33.6[29 a]
BWG week 1	3.2	2.7*	2.5**	2.0**	1.7	2.1	2.5**	2.8**
BWG week 0-13	12.2	10.5	12.6	10.7	8.6	9.0	9.7	9.2
BWG week 13-24	0.8	1.4	0.2	2.3	2.1	1.8	1.4	2.1
BWG week 24-52	0.8	0.3	0.8	-1.7	1.3	1.8	-0.7	1.2
BWG week 52-76	2.4	2.1	2.4	3.9	0.3	1.1	2.9	0.0
BWG week 76-102	-1.1	0.8	-2.8	-4.1	2.5	3.4	NC	1.5
BWG total	15.1	15.1	13.2	11.1	14.8 [a]	17.1 [a]	NC [a]	14.0 [a]
BWG % control	-	100	87	74	-	116	NC	95

Data adapted from Tables 3 and 4, pages 50 – 83, of Project No. 77-2061 (MRID 00130406)
* $p \leq 0.05$; ** $p \leq 0.01$
[a] Determined at Week 100 for female mice
Numbers in superscript are surviving mice at time interval
NL = Not legible
NC = Not calculated

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Although sporadic statistically significant effects were noted in treated male and female mice, none were dose- or treatment-related.

2. **Compound consumption:** The average time weighted compound consumption calculated by reviewer from legible data is in Table 1.

3. **Food efficiency:** No dose- or treatment-related effects were found on food efficiency during Weeks 0 - 14.

4. **Water consumption:** No dose- or treatment-related effects were found.

D. OPHTHALMOSCOPIC EXAMINATION:

Ophthalmoscopic examinations were not done.

E. BLOOD ANALYSES:

Hematology: No biologically or toxicologically relevant effects were noted on total RBC or WBC counts, HGB, HCT, or platelet counts. WBC differential counts were not located in the study report.

F. URINALYSIS:

Urinalysis was not done.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** As shown in Table 4, the terminal body weight of high-dose male mice at sacrifice was significantly decreased 9% relative to concurrent control mice, while that of mid- and high-dose female mice was increased 19% and 15%, respectively. The

decreased terminal body weight of high-dose male mice is associated with a 16% statistically significant decrease in the absolute liver weight relative to control in this group, however, the liver to body weight ratio of high-dose male mice was increased 7% (not statistically significant). In addition, the absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17%. Neither were statistically significant, and no microscopic histological correlates were found. Other sporadic absolute and/or relative to body weight organ weights were found, however, these were not considered toxicologically relevant as a dose-response was not evident.

The average body weights of mid- and high-dose female mice were increased 19% and 15% relative to concurrent controls at terminal sacrifice. While the absolute kidney weight of mid- and high-dose female mice were slightly increased 5% and 4%, respectively, the kidney to body weight ratio of these mice were increased 12% and 10%, respectively. No microscopic histological correlates were found. Other sporadic absolute and/or relative to body weight organ weights were found, however, these were not considered toxicologically relevant as a dose-response was not evident.

Table 4: Selected mean absolute (g) and relative (%) organ weights of CD-1 mice treated with glyphosate for 102 weeks

Organ	Dose (ppm)				Dose (ppm)			
	0	1000	5000	30,000	0	1000	5000	30,000
	Males				Females			
Kidney – Absolute								
Mean	0.693[20]	0.682[16]	0.666[16]	0.635[26]	0.489[20]	0.495[12]	0.513[27]	0.511[23]
SD	0.144	0.080	0.130	0.098	0.082	0.068	0.088	0.078
Kidney – Relative								
Mean	2.19	2.09	2.21	2.20	1.90	1.77	1.68*	1.71*
SD	0.47	0.22	0.46	0.29	0.27	0.23	0.24	0.23
Liver – Absolute								
Mean	1.753[20]	1.882[16]	1.488[17]	1.475*[26]	1.339[20]	1.521[12]	1.595[27]	1.393[23]
SD	0.483	1.156	0.179	0.319	0.316	0.401	0.443	0.213
Liver – Relative								
Mean	5.60	5.83	4.88	5.08	5.12	5.37	5.19	4.69
SD	1.80	3.79	0.52	0.95	0.85	1.10	1.19	0.83
Testis – Absolute								
Mean	0.157[20]	0.153[16]	0.158[17]	0.168[26]	-	-	-	-
SD	0.056	0.058	0.059	0.046				
Testis – Relative								
Mean	4.97	4.71	5.23	5.84	-	-	-	-
SD	1.80	1.81	2.10	1.58				
Spleen – Absolute								
Mean	0.089[20]	0.144[16]	0.067[17]	0.064[26]	0.099[20]	0.091[12]	0.136[27]	0.100[23]
SD	0.060	0.217	0.020	0.019	0.056	0.043	0.090	0.064
Spleen – Relative								
Mean	2.84	4.43	2.22	2.22	3.81	3.20	4.37	3.29
SD	2.00	6.59	0.63	0.69	2.05	1.44	2.81	1.98
BW – Terminal								
Mean	32[20]	33[16]	31[17]	29**[26]	26[20]	28[12]	31**[27]	30**[23]
SD	2	2	3	3	4	3	4	3

Data from Tables 15 and 16 on pages 127 - 135 of Project No. 77-2061 (MRID 00130406)
Numbers in superscript = N
* $p \leq 0.05$; ** $p \leq 0.01$

2. **Gross pathology:** No remarkable treatment-related effects were noted at necropsy.

3. **Microscopic pathology:**

   a. **Non-neoplastic**: The only treatment-related increases observed were in centrilobular hepatocyte hypertrophy of high-dose male mice as: 9/49 (18%), 5/50 (10%), 6/50 (6%), and 17/50 (34%) in the control, low-, mid-, and high-dose groups, respectively (no statistical significance). Centrilobular hepatocyte necrosis was significantly increased in high-dose male mice (2/49 (4%), 2/50 (4%), 2/50 (4%), and 10/50** (20%) in the control through high-dose groups, respectively, $p \leq 0.01$). The only non-neoplastic alteration in the urinary tract that occurred with an increased frequency was light-to-mild epithelial hyperplasia of the urinary bladder in males. The incidence was 6%, 6%, 20% and 16% in controls through high-dose, respectively. This was considered unrelated to treatment with glyphosate.
   No dose-related increases of centrilobular hepatocyte hypertrophy or necrosis were found in treated female mice. However, proximal tubular epithelial basophilia was significantly increased in high-dose female mice in comparison to controls.

   All other tissue alterations occurred sporadically or were considered spurious in distribution. Most were found with approximately equal frequency and severity in contro1 and treated animals, and were judged to be unrelated to glyphosate treatment.

   b. **Neoplastic:** Neoplastic outcomes were of the type commonly encountered in mice of this age and strain. Of the tumor types observed, bronchiolar-alveoli tumors of the lungs, hepatocellular neoplasms, and tumors of the lymphoreticular system, none were dose-related and were seen in all treatment groups (Table 5). Lymphoreticular tumors were more frequently observed in female mice, but the incidences were low and did not approach statistical significance. With the possible exception of kidney tumors (renal tubular adenomas) in males, all tumor types were considered spurious and unrelated to treatment. There were no other treatment-related increases in the incidence of neoplastic lesions, in particular hemangiosarcoma of the tissues/organs or systemic.

Table 5. Incidence of neoplasia in male and female mice treated with glyphosate for 24 months

Organ / Effect	Dose (ppm)			
	0	1000	5000	30,000
	Males			
Lung				
Bronchiolar alveolar adenoma	5/48	9/50	9/50	9/50
Bronchiolar alveolar adenocarcinoma	4/48	3/50	2/50	1/50
Lymphoblastic lymphosarcoma with leukemic manifestations	1/48	4/50	3/50	1/50
Liver				
Hepatocellular adenocarcinoma	5/49	4/50	6/50	4/50
Hepatocellular carcinoma	0/49	0/50	0/50	2/50
Lymph node (mediastinal)				
Lymphoblastic lymphosarcoma with leukemic manifestations	1/45	2/49	1/41	2/49
Kidney				
Renal tubular adenoma	0/49	0/49	1/50	3/50

Lymphoblastic lymphosarcoma with leukemic manifestations	1/49	3/49	2/50	2/50
	Females			
Lung				
Bronchiolar alveolar adenoma	10/49	9/50	10/49	1/50
Bronchiolar alveolar adenocarcinoma	1/49	3/50	4/49	4/50
Liver				
Hepatocellular adenocarcinoma	1/49	2/50	1/49	0/49
Composite lymphosarcoma	2/49	1/50	0/49	4/49

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

The study author(s) concluded that oral administration of glyphosate to mice at up to 30,000 ppm for 24 months resulted in slightly reduced body weight gain in high-dose males and females and several microscopic liver and kidney changes in high-dose males and females possibly related to test material administration. No changes in food consumption, clinical or gross necropsy observations and clinical chemistry parameters were noted, and no neoplasms considered to be related to glyphosate administration were observed. The oncogenic no-effect level was considered 30,000 ppm of glyphosate.

B. REVIEWER COMMENTS:

In this study, no significant treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weights of high-dose males were significantly decreased 9% while the absolute liver weights of high-dose males mice were significantly decreased 16%; however, no significant treatment-related effects were found on the liver to body weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17%. Neither were statistically significant, and no microscopic histological correlates were found. The incidence of centrilobular hepatocyte hypertrophy was slightly, but not significantly increased in high-dose male mice at terminal sacrifice or if all mice were included in the analyses. Centrilobular hepatocyte necrosis was significantly increased in high-dose male mice (2/49 (4%) control vs 10/50** (20%) in high-dose males ($p \leq 0.01$). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice. However, proximal tubular epithelial basophilia was significantly increased in high-dose female mice (0/50 (0%), 2/50 (4%), 4/50 (8%), and 9/50** (18%) in the control through high-dose groups, respectively, $p \leq 0.01$). All other tissue alterations occurred sporadically or were considered spurious in distribution and were found with approximately equal frequency and severity in contro1 and treated animals. These were considered unrelated to glyphosate treatment.

Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for

males and 6069 mg/kg bw/day for females). The NOAEL for the study was 5000 ppm (approximately 835 mg/kg bw/day for males and 968 mg/kg bw/day for females).

With the possible exception of kidney tumors (renal tubular adenomas) in males, there were no treatment-related increases in the incidence of neoplastic lesions, in particular hemangiosarcoma of the tissues/organs or systemically, induced by glyphosate treatment.

This carcinogenicity study in mice is **Acceptable / Non-guideline** and does not satisfy guideline requirements for a carcinogenicity study [OCSPP 870.4200; OECD 451] in mice. However, the study was conducted before establishment of OCSPP 870.4200 recommendations.

C. STUDY DEFICIENCIES:

The average time-weighted dose of Glyphosate in mg/kg bw/day to treated animals was not calculated. This is considered a minor deficiency.

Leukocyte differential counts, although reportedly done, were not located in the study report. This is considered a minor deficiency.

The larynx, rectum, and seminal vesicles were not collected at sacrifice for microscopic analyses. This is considered a minor deficiency.

Historical data on the incidences of non-neoplastic and neoplastic effects of control mice treated for two-years in the performing laboratory were not included in the study report. This is considered a minor deficiency.

Although the reviewer was provided with the “Best Document Available,” many portions of the study were difficult to read or were illegible.

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Akerman, Gregory
Sent: Wed 9/9/2015 5:34:52 PM
Subject: glyphosate CARC meeting

Hi Lori Since (I think) you send out the meeting invites for the CARC meetings, would you remind the CARC members that there is an extended CARC meeting next Wed and that the meeting materials are on the CARC dbase?

Thanks,

Greg

To: Schlosser, Christopher[Schlosser.Christopher@epa.gov]
From: Akerman, Gregory
Sent: Wed 9/9/2015 2:35:42 PM
Subject: RE: please add this draft doc to the carc dbase under glyphosate

Thank you!

From: Schlosser, Christopher
Sent: Wednesday, September 09, 2015 10:35 AM
To: Akerman, Gregory
Subject: RE: please add this draft doc to the carc dbase under glyphosate

Ok its there

From: Akerman, Gregory
Sent: Wednesday, September 09, 2015 10:33 AM
To: Schlosser, Christopher
Subject: please add this draft doc to the carc dbase under glyphosate

Thanks Chris!!

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Akerman, Gregory
Sent: Wed 9/9/2015 12:58:56 PM
Subject: RE: carc db

Ok.

From: Rowland, Jess
Sent: Wednesday, September 09, 2015 8:58 AM
To: Akerman, Gregory
Subject: RE: carc db

G

Ex. 5 - Deliberative Process

Sent from my Windows Phone

From: Akerman, Gregory
Sent: 9/9/2015 8:27 AM
To: Rowland, Jess
Subject: RE: carc db

Ex. 5 - Deliberative Process

From: Rowland, Jess
Sent: Tuesday, September 08, 2015 9:04 PM
To: Akerman, Gregory
Subject: carc db

G;

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Akerman, Gregory
Sent: Wed 9/9/2015 12:27:10 PM
Subject: RE: carc db

Ex. 5 - Deliberative Process

From: Rowland, Jess
Sent: Tuesday, September 08, 2015 9:04 PM
To: Akerman, Gregory
Subject: carc db

G;

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Akerman, Gregory
Sent: Wed 9/9/2015 11:57:09 AM
Subject: RE: carc db

Ok will do.

From: Rowland, Jess
Sent: Tuesday, September 08, 2015 9:04 PM
To: Akerman, Gregory
Subject: carc db

G;

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: McCarroll, Nancy[McCarroll.Nancy@epa.gov]
From: Akerman, Gregory
Sent: Wed 9/9/2015 11:01:53 AM
Subject: Will you please take a look at this for me?
Muta section for glyphosate CARC meeting 9.9.15.docx

Hi Nancy,

Ex. 5 - Deliberative Process

Thanks!!!

Greg

From: Akerman, Gregory
Location: S-10621
Importance: Normal
Subject: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 12:00:00 PM
End Date/Time: Thur 9/10/2015 1:00:00 PM

Jess asked me to set up this meeting on this date and time to prep for the glyphosate CARC meeting.

NOTE: Jess will be calling in for this meeting. Jess, you can call in using the following number:

Call in Number: Ex. 6 - Personal Privacy

Conf Code: Ex. 6 - Personal Privacy

To: Middleton, Karlyn[Middleton.Karlyn@epa.gov]
From: Akerman, Gregory
Sent: Wed 9/2/2015 5:03:52 PM
Subject: RE: CARC pre=meet for glyphosate

Sorry. I picked up the phone too slow. Yes, the meeting is next Thurs at 8 AM. Do you need me to resend the invite to you to add to your calendar?

From: Middleton, Karlyn
Sent: Wednesday, September 02, 2015 1:03 PM
To: Akerman, Gregory
Subject: RE: CARC pre=meet for glyphosate

I can make the meeting...it's at 8 right?

From: Akerman, Gregory
Sent: Monday, August 31, 2015 9:56 AM
To: Middleton, Karlyn
Subject: RE: CARC pre=meet for glyphosate

Karlyn,

Sorry, I told Jess that you are chair toxsac during that time, but he said he will only be in the office on Thurs morning. He said he wants to work with Anwar on how to present the data. He said it is not necessary that you be there for that. I'm not really sure if he wants me at the meeting, but asked me to set it up.

Greg

From: Middleton, Karlyn
Sent: Monday, August 31, 2015 9:31 AM
To: Akerman, Gregory
Subject: RE: CARC pre=meet for glyphosate

Greg,

I will be chairing the dicamba ToxSAC meeting during that time (9 -11).

-----Original Appointment-----
From: Akerman, Gregory
Sent: Monday, August 31, 2015 9:16 AM

To: Rowland, Jess; Dunbar, Anwar; Middleton, Karlyn
Subject: CARC pre=meet for glyphosate
When: Thursday, September 10, 2015 9:00 AM-10:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: S-10621

Jess asked me to set up this meeting on this date and time to prep for the glyphosate CARC meeting.

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Akerman, Gregory
Sent: Tue 9/1/2015 7:29:25 PM
Subject: RE: CARC pre=meet for glyphosate

Karlyn said she can't make it for the entire meeting but will try to stop by. Anwar accepted the invitation.

-----Original Appointment-----
From: Rowland, Jess
Sent: Tuesday, September 01, 2015 3:28 PM
To: Akerman, Gregory
Subject: Accepted: CARC pre=meet for glyphosate
When: Thursday, September 10, 2015 8:00 AM-9:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: S-10621

From: Akerman, Gregory
Location: S-10621
Importance: Normal
Subject: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 12:00:00 PM
End Date/Time: Thur 9/10/2015 1:00:00 PM

Jess asked me to set up this meeting on this date and time to prep for the glyphosate CARC meeting.

To: Middleton, Karlyn[Middleton.Karlyn@epa.gov]
From: Akerman, Gregory
Sent: Mon 8/31/2015 1:55:33 PM
Subject: RE: CARC pre=meet for glyphosate

Karlyn,

Sorry, I told Jess that you are chair toxsac during that time, but he said he will only be in the office on Thurs morning. He said he wants to work with Anwar on how to present the data. He said it is not necessary that you be there for that. I'm not really sure if he wants me at the meeting, but asked me to set it up.

Greg

From: Middleton, Karlyn
Sent: Monday, August 31, 2015 9:31 AM
To: Akerman, Gregory
Subject: RE: CARC pre=meet for glyphosate

Greg,

I will be chairing the dicamba ToxSAC meeting during that time (9 -11).

-----Original Appointment-----
From: Akerman, Gregory
Sent: Monday, August 31, 2015 9:16 AM
To: Rowland, Jess; Dunbar, Anwar; Middleton, Karlyn
Subject: CARC pre=meet for glyphosate
When: Thursday, September 10, 2015 9:00 AM-10:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: S-10621

Jess asked me to set up this meeting on this date and time to prep for the glyphosate CARC meeting.

From: Akerman, Gregory
Location: S-10621
Importance: Normal
Subject: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 1:00:00 PM
End Date/Time: Thur 9/10/2015 2:00:00 PM

Jess asked me to set up this meeting on this date and time to prep for the glyphosate CARC meeting.

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Akerman, Gregory
Sent: Fri 8/28/2015 5:14:47 PM
Subject: RE: Glyphosate CARC document

Ex. 5 - Deliberative Process

From: Rowland, Jess
Sent: Friday, August 28, 2015 12:45 PM
To: Akerman, Gregory
Subject: FW: Glyphosate CARC document

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Lobdell, Danelle
Sent: Thursday, August 20, 2015 4:38 PM
To: Rowland, Jess
Subject: RE: Glyphosate CARC document

Hi Jess,

Ex. 5 - Deliberative Process

Danelle

Danelle T. Lobdell, Ph.D., M.S.

Epidemiologist

National Health and Environmental Effects Research Laboratory

Environmental Public Health Division

Mail:

USEPA

MD 58A

Research Triangle Park, NC 27711

Package Delivery:

USEPA Human Studies Facility

104 Mason Farm Rd, Room 52

Chapel Hill, NC 27514-4512

Phone: 919-843-4434 Fax: 919-966-7584

From: Rowland, Jess
Sent: Thursday, August 20, 2015 9:53 AM
To: Lobdell, Danelle
Subject: RE: Glyphosate CARC document

I will call you

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Lobdell, Danelle
Sent: Thursday, August 20, 2015 9:52 AM
To: Rowland, Jess
Subject: RE: Glyphosate CARC document

Hi Jess,

Yes, 10:30 works for me. Do you want to call me or should I call you?

Danelle

Danelle T. Lobdell, Ph.D., M.S.

Epidemiologist

National Health and Environmental Effects Research Laboratory

Environmental Public Health Division

Mail:

USEPA

MD 58A

Research Triangle Park, NC 27711

Package Delivery:

USEPA Human Studies Facility

104 Mason Farm Rd, Room 52

Chapel Hill, NC 27514-4512

Phone: 919-843-4434 Fax: 919-966-7584

From: Rowland, Jess
Sent: Thursday, August 20, 2015 9:42 AM
To: Lobdell, Danelle
Subject: Glyphosate CARC document
Importance: High

Hi Danelle

Here is the outline for the Epi section of the CARC document.

I have put in some text to lead into your assessment.

I am free from 10:30 to 11:00 am. Is this a suitable time for us to discuss…

Thanks

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Kidwell, Jessica[kidwell.jessica@epa.gov]
From: Akerman, Gregory
Sent: Thur 7/30/2015 4:19:54 PM
Subject: FW: Glyphosate - IARC Monograph
IARC Monograph.pdf

I guess he forgot to add your name.

From: Rowland, Jess
Sent: Wednesday, July 29, 2015 1:47 PM
To: Akerman, Gregory; Dunbar, Anwar; Middleton, Karlyn; Wood, Charles; Lobdell, Danelle; Morton, Thurston
Cc: Housenger, Jack
Subject: Glyphosate - IARC Monograph

Hi Greg et al

Attached is the IARC Monograph. Perfect timing.

This will help us in the preparation of the CARC document.

Should be any trouble reading it……only 92 pages…!!

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

GLYPHOSATE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 1071-83-6 (acid); also relevant:
38641-94-0 (glyphosate-isopropylamine salt)
40465-66-5 (monoammonium salt)
69254-40-6 (diammonium salt)
34494-03-6 (glyphosate-sodium)
81591-81-3 (glyphosate-trimesium)

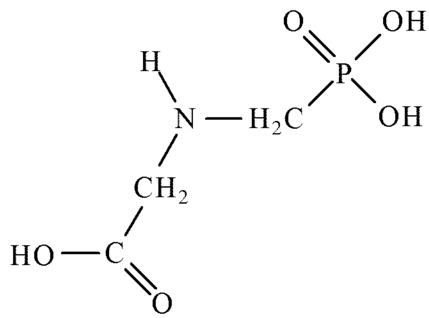
Chem. Abstr. Serv. Name: *N*-(phosphonomethyl)glycine

Preferred IUPAC Name: *N*-(phosphonomethyl)glycine

Synonyms: Gliphosate; glyphosate; glyphosate hydrochloride; glyphosate [calcium, copper (2+), dilithium, disodium, magnesium, monoammonium, monopotassium, monosodium, sodium, or zinc] salt

Trade names: Glyphosate products have been sold worldwide under numerous trade names, including: Abundit Extra; Credit; Xtreme; Glifonox; Glyphogan; Ground-Up; Rodeo; Roundup; Touchdown; Tragli; Wipe Out; Yerbimat (Farm Chemicals International, 2015).

1.1.2 Structural and molecular formulae and relative molecular mass



Molecular formula: $C_3H_8NO_5P$
Relative molecular mass: 169.07

Additional information on chemical structure is also available in the PubChem Compound database (NCBI, 2015).

1.1.3 Chemical and physical properties of the pure substance

Description: Glyphosate acid is a colourless, odourless, crystalline solid. It is formulated as a salt consisting of the deprotonated acid of glyphosate and a cation (isopropylamine, ammonium, or sodium), with more than one salt in some formulations.

Solubility: The acid is of medium solubility at 11.6 g/L in water (at 25 °C) and insoluble in common organic solvents such as acetone, ethanol, and xylene; the alkali-metal and amine salts are readily soluble in water (Tomlin, 2000).

Volatility: Vapour pressure, 1.31 × 10^{-2} mPa at 25 °C (negligible) (Tomlin, 2000).

Stability: Glyphosate is stable to hydrolysis in the range of pH 3 to pH 9, and relatively stable to photodegradation (Tomlin, 2000). Glyphosate is not readily hydrolysed or oxidized in the field (Rueppel *et al.* 1977). It decomposes on heating, producing toxic fumes that include nitrogen oxides and phosphorus oxides (IPCS, 2005).

Reactivity: Attacks iron and galvanized steel (IPCS, 2005).

Octanol/water partition coefficient (P): log P, < −3.2 (pH 2–5, 20 °C) (OECD method 107) (Tomlin, 2000).

Henry's law: < 2.1 × 10^{-7} Pa m^3 mol^{-1} (Tomlin, 2000).

Conversion factor: Assuming normal temperature (25 °C) and pressure (101 kPa), mg/m^3 = 6.92 × ppm.

1.1.4 *Technical products and impurities*

Glyphosate is formulated as an isopropylamine, ammonium, or sodium salt in water-soluble concentrates and water-soluble granules. The relevant impurities in glyphosate technical concentrates are formaldehyde (maximum, 1.3 g/kg), *N*-nitrosoglyphosate (maximum, 1 mg/kg), and *N*-nitroso-*N*-phosphonomethylglycine (FAO, 2000). Surfactants and sulfuric and phosphoric acids may be added to formulations of glyphosate, with type and concentration differing by formulation (IPCS, 1994).

1.2 Production and use

1.2.1 *Production*

(a) *Manufacturing processes*

Glyphosate was first synthesized in 1950 as a potential pharmaceutical compound, but its herbicidal activity was not discovered until it was re-synthesized and tested in 1970 (Székács & Darvas, 2012). The isopropylamine, sodium, and ammonium salts were introduced in 1974, and the trimesium (trimethylsulfonium) salt was introduced in Spain in 1989. The original patent protection expired outside the USA in 1991, and within the USA in 2000. Thereafter, production expanded to other major agrochemical manufacturers in the USA, Europe, Australia, and elsewhere (including large-scale production in China), but the leading preparation producer remained in the USA (Székács & Darvas, 2012).

There are two dominant families of commercial production of glyphosate, the "alkyl ester" pathways, predominant in China, and the "iminodiacetic acid" pathways, with iminodiacetic acid produced from iminodiacetonitrile (produced from hydrogen cyanide), diethanol amine, or chloroacetic acid (Dill *et al.*, 2010; Tian *et al.*, 2012).

To increase the solubility of technical-grade glyphosate acid in water, it is formulated as its isopropylamine, monoammonium, potassium, sodium, or trimesium salts. Most common is the isopropylamine salt, which is formulated as a liquid concentrate (active ingredient, 5.0–62%), ready-to-use liquid (active ingredient, 0.5–20%), pressurized liquid (active ingredient, 0.75–0.96%), solid (active ingredient, 76–94%), or pellet/tablet (active ingredient, 60–83%) (EPA, 1993a).

There are reportedly more than 750 products containing glyphosate for sale in the USA alone (NPIC, 2010). Formulated products contain various non-ionic surfactants, most notably polyethyloxylated tallowamine (POEA), to facilitate uptake by plants (Székács & Darvas, 2012). Formulations might contain other active ingredients, such as simasine, 2,4-dichlorophenoxyacetic acid (2,4-D), or 4-chloro-2-methylphenoxyacetic acid (IPCS, 1996), with herbicide resistance driving demand for new herbicide formulations containing multiple active ingredients (Freedonia, 2012).

(b) Production volume

Glyphosate is reported to be manufactured by at least 91 producers in 20 countries, including 53 in China, 9 in India, 5 in the USA, and others in Australia, Canada, Cyprus, Egypt, Germany, Guatemala, Hungary, Israel, Malaysia, Mexico, Singapore, Spain, Taiwan (China), Thailand, Turkey, the United Kingdom, and Venezuela (Farm Chemicals International, 2015). Glyphosate was registered in over 130 countries as of 2010 and is probably the most heavily used herbicide in the world, with an annual global production volume estimated at approximately 600 000 tonnes in 2008, rising to about 650 000 tonnes in 2011, and to 720 000 tonnes in 2012 (Dill *et al.*, 2010; CCM International, 2011; Hilton, 2012; Transparency Market Research, 2014).

Production and use of glyphosate have risen dramatically due to the expiry of patent protection (see above), with increased promotion of non-till agriculture, and with the introduction in 1996 of genetically modified glyphosate-tolerant crop varieties (Székács & Darvas, 2012). In the USA alone, more than 80 000 tonnes of glyphosate were used in 2007 (rising from less than 4000 tonnes in 1987) (EPA, 1997, 2011). This rapid growth rate was also observed in Asia, which accounted for 30% of world demand for glyphosate in 2012 (Transparency Market Research, 2014). In India, production increased from 308 tonnes in 2003–2004, to 2100 tonnes in 2007–2008 (Ministry of Chemicals & Fertilizers, 2008). China currently produces more than 40% of the global supply of glyphosate, exports almost 35% of the global supply (Hilton, 2012), and reportedly has sufficient production capacity to satisfy total global demand (Yin, 2011).

1.2.2 Uses

Glyphosate is a broad-spectrum, post-emergent, non-selective, systemic herbicide, which effectively kills or suppresses all plant types, including grasses, perennials, vines, shrubs, and trees. When applied at lower rates, glyphosate is a plant-growth regulator and desiccant. It has agricultural and non-agricultural uses throughout the world.

(a) Agriculture

Glyphosate is effective against more than 100 annual broadleaf weed and grass species, and more than 60 perennial weed species (Dill *et al.*, 2010). Application rates are about 1.5–2 kg/ha for pre-harvest, post-planting, and pre-emergence use; about 4.3 kg/ha as a directed spray in vines, orchards, pastures, forestry, and industrial weed control; and about 2 kg/ha as an aquatic herbicide (Tomlin, 2000). Common application methods include broadcast, aerial, spot, and directed spray applications (EPA, 1993a).

Due to its broad-spectrum activity, the use of glyphosate in agriculture was formerly limited to post-harvest treatments and weed control between established rows of tree, nut, and vine crops. Widespread adoption of no-till and conservation-till practices (which require chemical weed control while reducing soil erosion and labour and fuel costs) and the introduction of transgenic crop varieties engineered to be resistant to glyphosate have transformed glyphosate to a post-emergent, selective herbicide for use on annual crops (Duke & Powles, 2009; Dill *et al.* 2010). Glyphosate-resistant transgenic varieties have been widely adopted for the production of corn, cotton, canola, and soybean (Duke & Powles, 2009). Production of such crops accounted for 45% of worldwide demand for glyphosate in 2012 (Transparency Market Research, 2014). However, in Europe, where the planting of genetically modified crops has been largely restricted, post-harvest treatment is still the most common application of glyphosate (Glyphosate Task Force, 2014). Intense and continuous use of glyphosate has led to the emergence of resistant weeds that may reduce its effectiveness (Duke & Powles, 2009).

(b) Residential use

Glyphosate is widely used for household weed control throughout the world. In the USA, glyphosate was consistently ranked as the second most commonly used pesticide (after 2,4-D) in the home and garden market sector between 2001 and 2007, with an annual use of 2000–4000 tonnes (EPA, 2011).

(c) Other uses

Glyphosate was initially used to control perennial weeds on ditch banks and roadsides and under power lines (Dill *et al.*, 2010). It is also used to control invasive species in aquatic or wetland systems (Tu *et al.*, 2001). Approximately 1–2% of total glyphosate use in the USA is in forest management (Mance, 2012).

Glyphosate has been used in a large-scale aerial herbicide-spraying programme begun in 2000 to reduce the production of cocaine in Colombia (Lubick, 2009), and of marijuana in Mexico and South America (Székács & Darvas, 2012).

(d) Regulation

Glyphosate has been registered for use in at least 130 countries (Dill *et al.*, 2010). In the USA, all uses are eligible for registration on the basis of a finding that glyphosate "does not pose unreasonable risks or adverse effects to humans or the environment" (EPA, 1993a). A review conducted in 2001 in connection with the registration process in the European Union reached similar conclusions regarding animal and human safety, although the protection of groundwater during non-crop use was identified as requiring particular attention in the short term (European Commission, 2002).

Nevertheless, as worldwide rates of adoption of herbicide-resistant crops and of glyphosate use have risen in recent years (Duke & Powles, 2009), restriction of glyphosate use has been enacted or proposed in several countries, although documented actions are few. In 2013, the Legislative Assembly of El Salvador voted a ban on the use of pesticides containing glyphosate (República de El Salvador, 2013). Sri Lanka is reported to have instituted a partial ban based on an increasing number of cases of chronic kidney disease among agricultural workers, but the ban was lifted after 2 months (ColomboPage, 2014). The reasons for such actions have included the development of resistance among weed species, as well as health concerns.

No limits for occupational exposure were identified by the Working Group.

1.3 Measurement and analysis

Several methods exist for the measurement of glyphosate and its major metabolite aminomethyl phosphonic acid (AMPA) in various media, including air, water, urine, and serum (Table 1.1). The methods largely involve derivatization with 9-fluorenylmethyl chloro formate (FMOC-Cl) to reach sufficient retention in chromatographic columns (Kuang *et al.*, 2011; Botero-Coy *et al.*, 2013). Chromatographic techniques that do not require derivatization and enzyme-linked immunosorbent assays (ELISA) are under development (Sanchís *et al.*, 2012).

Table 1.1 Methods for the analysis of glyphosate

Sample matrix	Assay procedure	Limit of detection	Reference
Water	HPLC/MS (with online solid-phase extraction)	0.08 µg/L	Lee *et al.* (2001)
	ELISA	0.05 µg/L	Abraxis (2005)
	LC-LC-FD	0.02 µg/L	Hidalgo *et al.* (2004)
	Post HPLC column derivatization and FD	6.0 µg/L	EPA (1992)
	UV visible spectrophotometer (at 435 ng)	1.1 µg/L	Jan *et al.* (2009)
Soil	LC–MS/MS with triple quadrupole	0.02 mg/kg	Botero-Coy *et al.* (2013)
Dust	GC-MS-MID	0.0007 mg/kg	Curwin *et al.* (2005)
Air	HPLC/MS with online solid-phase extraction	0.01 ng/m³	Chang *et al.* (2011)
Fruits and vegetables	HILIC/WAX with ESI-MS/MS	1.2 µg/kg	Chen *et al.* (2013)
Field crops (rice, maize and soybean)	LC–ESI-MS/MS	0.007–0.12 mg/kg	Botero-Coy *et al.* (2013b)
Plant vegetation	HPLC with single polymeric amino column	0.3 mg/kg	Nedelkoska & Low (2004)
Serum	LC–MS/MS	0.03 µg/mL 0.02 µg/mL (aminomethylphosphonic acid) 0.01 µg/mL (3-methylphosphinicopropionic acid)	Yoshioka *et al.* (2011)
Urine	HPLC with post-column reaction and FD	1 µg/L	Acquavella *et al.* (2004)
	ELISA	0.9 µg/L	Curwin *et al.* (2007)

ELISA, enzyme-linked immunosorbent assay; ESI-MS/MS, electrospray tandem mass spectrometry; FD, fluorescence detection; GC-MS-MID, gas chromatography-mass spectrometry in multiple ion detection mode; HILIC/WAX, hydrophilic interaction/weak anion-exchange liquid chromatography; HPLC/MS, high-performance liquid chromatography with mass spectrometry; HPLC, high-performance liquid chromatography; LC-ESI–MS/MS, liquid chromatography-electrospray–tandem mass spectrometry; LC–LC, coupled-column liquid chromatography; LC–MS/MS, liquid chromatography–tandem mass spectrometry

1.4 Occurrence and exposure

1.4.1 Exposure

(a) Occupational exposure

Studies related to occupational exposure to glyphosate have included farmers and tree nursery workers in the USA, forestry workers in Canada and Finland, and municipal weed-control workers in the United Kingdom (Centre de Toxicologie du Québec, 1988; Jauhiainen *et al.*, 1991; Lavy *et al.*, 1992; Acquavella *et al.*, 2004; Johnson *et al.*, 2005). Para-occupational exposures to glyphosate have also been measured in farming families (Acquavella *et al.*, 2004; Curwin *et al.*, 2007). These studies are summarized in Table 1.2.

(b) Community exposure

Glyphosate can be found in soil, air, surface water, and groundwater (EPA, 1993a). Once in the environment, glyphosate is adsorbed to soil and is broken down by soil microbes to AMPA (Borggaard & Gimsing, 2008). In surface water, glyphosate is not readily broken down by water or sunlight (EPA, 1993a). Despite extensive worldwide use, there are relatively few studies

Table 1.2 Occupational and para-occupational exposure to glyphosate

Industry, country, year	Job/process	Results	Comments/additional data	Reference
Forestry				
Canada, 1986		Arithmetic mean of air glyphosate concentrations:	Air concentrations of glyphosate were measured at the work sites of one crew (five workers) during ground spraying 268 urine samples were collected from 40 workers; glyphosate concentration was above the LOD (15 μg/L) in 14%	Centre de Toxicologie du Québec (1988)
	Signaller	Morning, 0.63 μg/m ^{3} Afternoon, 2.25 μg/m ^{3}		
	Operator	Morning, 1.43 μg/m ^{3} Afternoon, 6.49 μg/m ^{3}		
	Overseer	Morning, 0.84 μg/m ^{3} Afternoon, 2.41 μg/m ^{3}		
	Mixer	Morning, 5.15 μg/m ^{3} Afternoon, 5.48 μg/m ^{3}		
Finland, year NR	Workers performing silvicultural clearing (*n* = 5)	Range of air glyphosate concentrations, < 1.25–15.7 μg/m ^{3} (mean, NR)	Clearing work was done with brush saws equipped with pressurized herbicide sprayers Air samples were taken from the workers' breathing zone (number of samples, NR) Urine samples were collected during the afternoons of the working week (number, NR) Glyphosate concentrations in urine were below the LOD (10 μg/L)	Jauhiainen *et al.* (1991)
USA, year NR	Workers in two tree nurseries (*n* = 14)	In dermal sampling, 1 of 78 dislodgeable residue samples were positive for glyphosate The body portions receiving the highest exposure were ankles and thighs	Dermal exposure was assessed with gauze patches attached to the clothing and hand rinsing Analysis of daily urine samples repeated over 12 weeks was negative for glyphosate	Lavy *et al.* (1992)
Weed control				
United Kingdom, year NR	Municipal weed control workers (*n* = 18)	Median, 16 mg/m ^{3} in 85% of 21 personal air samples for workers spraying with mechanized all-terrain vehicle Median, 0.12 mg/m ^{3} in 33% of 12 personal air samples collected from workers with backpack with lance applications	[The Working Group noted that the reported air concentrations were substantially higher than in other studies, but was unable to confirm whether the data were for glyphosate or total spray fluid] Dermal exposure was also measured, but reported as total spray fluid, rather than glyphosate	Johnson *et al.* (2005)

Table 1.2 (continued)

Industry, country, year	Job/process	Results	Comments/additional data	Reference
Farming				
USA, 2001	Occupational and para-occupational exposure of 24 farm families (24 fathers, 24 mothers and 65 children). Comparison group: 25 non-farm families (23 fathers, 24 mothers and 51 children)	Geometric mean (range) of glyphosate concentrations in urine: Non-farm fathers, 1.4 µg/L (0.13–5.4) Farm fathers, 1.9 µg/L (0.02–18) Non-farm mothers, 1.2 µg/L (0.06–5.0) Farm mothers, 1.5 µg/L (0.10–11) Non-farm children, 2.7 µg/L (0.10–9.4) Farm children, 2.0 µg/L (0.02–18)	Frequency of glyphosate detection ranged from 66% to 88% of samples (observed concentrations below the LOD were not censored). Detection frequency and geometric mean concentration were not significantly different between farm and non-farm families (observed concentrations below the LOD were not censored)	Curwin *et al.* (2007)
USA, year NR	Occupational and para-occupational exposures of 48 farmers, their spouses, and 79 children	Geometric mean (range) of glyphosate concentration in urine on day of application: Farmers, 3.2 µg/L (< 1 to 233 µg/L) Spouses, NR (< 1 to 3 µg/L) Children, NR (< 1 to 29 µg/L)	24-hour composite urine samples for each family member the day before, the day of, and for 3 days after a glyphosate application. Glyphosate was detected in 60% of farmers' samples, 4% of spouses' samples and 12% of children's samples the day of spraying and in 27% of farmers' samples, 2% of spouses' samples and 5% of children's samples 3 days after	Acquavella *et al.* (2004)

LOD, limit of detection; ND, not detected; NR, not reported on the environmental occurrence of glyphosate (Kolpin *et al.*, 2006).

(i) Air

Very few studies of glyphosate in air were available to the Working Group. Air and rainwater samples were collected during two growing seasons in agricultural areas in Indiana, Mississippi, and Iowa, USA (Chang *et al.*, 2011). The frequency of glyphosate detection ranged from 60% to 100% in air and rain samples, and concentrations ranged from < 0.01 to 9.1 ng/m^3 in air samples and from < 0.1 to 2.5 µg/L in rainwater samples. Atmospheric deposition was measured at three sites in Alberta, Canada. Rainfall and particulate matter were collected as total deposition at 7-day intervals throughout the growing season. Glyphosate deposition rates ranged from < 0.01 to 1.51 µg/m^2 per day (Humphries *et al.*, 2005).

No data were available to the Working Group regarding glyphosate concentrations in indoor air.

(ii) Water

Glyphosate in the soil can leach into groundwater, although the rate of leaching is believed to be low (Borggaard & Gimsing, 2008; Simonsen *et al.*, 2008). It can also reach surface waters by direct emission, atmospheric deposition, and by adsorption to soil particles suspended in runoff water (EPA, 1993a; Humphries *et al.*, 2005). Table 1.3 summarizes data on concentrations of glyphosate or AMPA in surface water and groundwater.

(iii) Residues in food and dietary intake

Glyphosate residues have been measured in cereals, fruits, and vegetables (Table 1.4). Residues were detected in 0.04% of 74 305 samples of fruits, vegetables, and cereals tested from 27 member states of the European Union, and from Norway, and Iceland in 2007 (EFSA, 2009). In cereals, residues were detected in 50% of samples tested in Denmark in 1998–1999, and in 9.5% of samples tested from member states of the European Union, and from Norway and Iceland in 2007 (Granby & Vahl, 2001; EFSA, 2009). In the United Kingdom, food sampling for glyphosate residues has concentrated mainly on cereals, including bread and flour. Glyphosate has been detected regularly and usually below the reporting limit (Pesticide Residues Committee, 2007, 2008, 2009, 2010). Six out of eight samples of tofu made from Brazilian soy contained glyphosate, with the highest level registered being 1.1 mg/kg (Pesticide Residues Committee, 2007).

(iv) Household exposure

In a survey of 246 California households, 14% were found to possess at least one product containing glyphosate (Guha *et al.*, 2013).

(v) Biological markers

Glyphosate concentrations in urine were analysed in urban populations in Europe, and in a rural population living near areas sprayed for drug eradication in Colombia (MLHB, 2013; Varona *et al.*, 2009). Glyphosate concentrations in Colombia were considerably higher than in Europe, with means of 7.6 ng/L and 0.02 µg/L, respectively (Table 1.5). In a study in Canada, glyphosate concentrations in serum ranged from undetectable to 93.6 ng/mL in non-pregnant women (n = 39), and were undetectable in serum of pregnant women (n = 30) and fetal cord serum (Aris & Leblanc, 2011).

1.4.2 Exposure assessment

Exposure assessment methods in epidemiological studies on glyphosate and cancer are discussed in Section 2.0 of the *Monograph* on Malathion, in the present volume.

Table 1.3 Concentration of glyphosate and AMPA in water

Country, year of sampling	Number of samples/setting	Results	Comments/additional data	Reference
USA, 2002	51 streams/agricultural areas (154 samples)	Maximum glyphosate concentration, 5.1 μg/L Maximum AMPA concentration, 3.67 μg/L	The samples were taken following pre- and post-emergence application and during harvest season Glyphosate detected in 36% of samples; AMPA detected in 69% of samples	Battaglin *et al.* (2005)
USA, 2002	10 wastewater treatment plants and two reference streams (40 samples)	Glyphosate, range ≤ 0.1–2 μg/L AMPA, range ≤ 0.1–4 μg/L	AMPA was detected more frequently (67.5%) than glyphosate (17.5%)	Kolpin *et al.* (2006)
Canada, 2002	3 wetlands and 10 agricultural streams (74 samples)	Range, < 0.02–6.08 μg/L	Glyphosate was detected in most of the wetlands and streams (22% of samples)	Humphries *et al.* (2005)
Colombia, year NR	5 areas near crops and coca eradication (24 samples)	Maximum concentration, 30.1 μg/L (minimum and mean, NR)	Glyphosate detected in 8% of samples (MDL, 25 μg/L)	Solomon *et al.* (2007)
Denmark, 2010–2012	4 agricultural sites (450 samples)	Range, < 0.1–31.0 μg/L	Glyphosate detected in 23% of samples; AMPA detected in 25% of samples	Brüch *et al.* (2013)

AMPA, aminomethylphosphonic acid; MDL, method detection limit; NR, data not reported

Table 1.4 Concentrations of glyphosate in food

Country, year	Type of food	Results	Comments/additional data	Reference
Denmark, 1998, 1999	Cereals	> 50% of samples had detectable residues Means: 0.08 mg/kg in 1999 and 0.11 mg/kg in 1998	49 samples of the 1998 harvest 46 samples of the 1999 harvest	Granby & Vahl (2001)
27 European Union member states, Norway and Iceland, 2007	350 different food commodities	0.04% of 2302 fruit, vegetable and cereal samples 9.5% of 409 cereal samples	74 305 total samples	EFSA (2009)
Australia, 2006	Composite sample of foods consumed in 24 hours	75% of samples had detectable residues Mean, 0.08 mg/kg Range, < 0.005 to 0.5 mg/kg	20 total samples from 43 pregnant women	McQueen *et al.* (2012)

Table 1.5 Concentrations of glyphosate and AMPA in urine and serum in the general population

Country, period	Subjects	Results	Comments/additional data	Reference
Urine				
18 European countries, 2013	162 individuals	Arithmetic mean of glyphosate concentration: 0.21 µg/L (maximum, 1.56 µg/L) Arithmetic mean of AMPA concentration: 0.19 µg/L (maximum, 2.63 µg/L)	44% of samples had quantifiable levels of glyphosate and 36% had quantifiable levels of AMPA	MLHB (2013)
Colombia, 2005–2006	112 residents of areas sprayed for drug eradication	Arithmetic mean (range) of glyphosate concentration: 7.6 µg/L (ND–130 µg/L) Arithmetic mean (range) of AMPA concentration: 1.6 µg/L (ND–56 µg/L)	40% of samples had detectable levels of glyphosate and 4% had detectable levels of AMPA (LODs, 0.5 and 1.0 µg/L, respectively) Urinary glyphosate was associated with use in agriculture	Varona *et al.* (2009)
Serum				
Canada, NR	30 pregnant women and 39 non-pregnant women	ND in serum of pregnant women or cord serum; Arithmetic mean, 73.6 µg/L, (range, ND–93.6 µg/L) in non-pregnant women	No subject had worked or lived with a spouse working in contact with pesticides LOD, 15 µg/L	Aris & Leblanc (2011)

AMPA, aminomethylphosphonic acid; LOD, limit of detection; ND, not detected; NR, not reported

2. Cancer in Humans

2.0 General discussion of epidemiological studies

A general discussion of the epidemiological studies on agents considered in Volume 112 of the *IARC Monographs* is presented in Section 2.0 of the *Monograph* on Malathion.

2.1 Cohort studies

See Table 2.1

The Agricultural Health Study (AHS), a large prospective cohort study conducted in Iowa and North Carolina in the USA, is the only cohort study to date to have published findings on exposure to glyphosate and the risk of cancer at many different sites (Alavanja *et al.*, 1996; NIH, 2015) (see Section 2.0 of the *Monograph* on Malathion, in the present volume, for a detailed description of this study).

The enrolment questionnaire from the AHS sought information on the use of 50 pesticides (ever or never exposure), crops grown and livestock raised, personal protective equipment used, pesticide application methods used, other agricultural activities and exposures, nonfarm occupational exposures, and several lifestyle, medical, and dietary variables. The duration (years) and frequency (days per year) of use was investigated for 22 of the 50 pesticides in the enrolment questionnaire. [Blair *et al.* (2011) assessed the possible impact of misclassification of occupational pesticide exposure on relative risks, demonstrating that nondifferential exposure misclassification biases relative risk estimates towards the null in the AHS and tends to decrease the study power.]

The first report of cancer incidence associated with pesticide use in the AHS cohort considered cancer of the prostate (Alavanja *et al.*, 2003). Risk estimates for exposure to glyphosate were not presented, but no significant exposure–response association with cancer of the prostate was found. In an updated analysis of the AHS (1993 to 2001), De Roos *et al.* (2005a) (see below) also found no association between exposure to glyphosate and cancer of the prostate (relative risk, RR, 1.1; 95% CI, 0.9–1.3) and no exposure–response trend (*P* value for trend = 0.69).

De Roos *et al.* (2005a) also evaluated associations between exposure to glyphosate and the incidence of cancer at several other sites. The prevalence of ever-use of glyphosate was 75.5% (> 97% of users were men). In this analysis, exposure to glyphosate was defined as: (a) ever personally mixed or applied products containing glyphosate; (b) cumulative lifetime days of use, or "cumulative exposure days" (years of use × days/year); and (c) intensity-weighted cumulative exposure days (years of use × days/year × estimated intensity level). Poisson regression was used to estimate exposure–response relations between exposure to glyphosate and incidence of all cancers combined, and incidence of 12 cancer types: lung, melanoma, multiple myeloma, and non-Hodgkin lymphoma (see Table 2.1) as well as oral cavity, colon, rectum, pancreas, kidney, bladder, prostate, and leukaemia (results not tabulated). Exposure to glyphosate was not associated with all cancers combined (RR, 1.0; 95% CI, 0.9–1.2; 2088 cases). For multiple myeloma, the relative risk was 1.1 (95% CI, 0.5–2.4; 32 cases) when adjusted for age, but was 2.6 (95% CI, 0.7–9.4) when adjusted for multiple confounders (age, smoking, other pesticides, alcohol consumption, family history of cancer, and education); in analyses by cumulative exposure-days and intensity-weighted exposure-days, the relative risks were around 2.0 in the highest tertiles. Furthermore, the association between multiple myeloma and exposure to glyphosate only appeared within the subgroup for which complete data were available on all the covariates; even without any adjustment, the risk of multiple myeloma associated with glyphosate use was increased by twofold among the smaller subgroup with available covariate data

Table 2.1 Cohort studies of cancer and exposure to glyphosate

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
De Roos *et al.* (2005a) Iowa and North Carolina, USA 1993–2001	54 315 (after exclusions, from a total cohort of 57 311) licensed pesticide applicators Exposure assessment method: questionnaire; semi-quantitative assessment from self-administered questionnaire	Lung	Ever use	147	0.9 (0.6–1.3)	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education	AHS Cancer sites investigated: lung, melanoma, multiple myeloma and NHL (results tabulated) as well as oral cavity, colon, rectum, pancreas, kidney, bladder, prostate and leukaemia (results not tabulated) [Strengths: large cohort; specific assessment of glyphosate; semiquantitative exposure assessment. Limitations: risk estimates based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]
			Cumulative exposure days:				
			1–20	40	1 (ref.)		
			21–56	26	0.9 (0.5–1.5)		
			57–2678	26	0.7 (0.4–1.2)		
			Trend-test *P* value: 0.21				
		Melanoma	Ever use	75	1.6 (0.8–3)		
			1–20	23	1 (ref.)		
			21–56	20	1.2 (0.7–2.3)		
			57–2678	14	0.9 (0.5–1.8)		
			Trend-test *P* value: 0.77				
		Multiple myeloma	Ever use	32	1.1 (0.5–2.4)		
			Ever use	32	2.6 (0.7–9.4)	Age only (results in this row only)	
			1–20	8	1 (ref.)		
			21–56	5	1.1 (0.4–3.5)		
			Trend-test *P* value: 0.27				
		NHL	Ever use	92	1.1 (0.7–1.9)		
			1–20	29	1 (ref.)		
			21–56	15	0.7 (0.4–1.4)		
			57–2678	17	0.9 (0.5–1.6)		
			Trend-test *P* value: 0.73				

Table 2.1 (continued)

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Flower *et al.* (2004) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up, 1975–1998	21 375; children (aged < 19 years) of licensed pesticide applicators in Iowa (n = 17 357) and North Carolina (n = 4018) Exposure assessment method: questionnaire	Childhood cancer	Maternal use of glyphosate (ever)	13	0.61 (0.32–1.16)	Child's age at enrolment	AHS Glyphosate results relate to the Iowa participants only [Strengths: Large cohort; specific assessment of glyphosate. Limitations: based on self-reported exposure; potential exposure to multiple pesticides; limited power for glyphosate exposure]
			Paternal use of glyphosate (prenatal)	6	0.84 (0.35–2.34)		
Engel *et al.* (2005) Iowa and North Carolina, USA Enrolment, 1993–1997 follow-up to 2000	30 454 wives of licensed pesticide applicators with no history of breast cancer at enrolment Exposure assessment method: questionnaire	Breast	Direct exposure to glyphosate	82	0.9 (0.7–1.1)	Age, race, state	AHS [Strengths: large cohort; specific assessment of glyphosate. Limitations: based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]
			Husband's use of glyphosate	109	1.3 (0.8–1.9)		
Lee *et al.* (2007) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up to 2002	56 813 licensed pesticide applicators Exposure assessment method: questionnaire	Colorectum	Exposed to glyphosate	225	1.2 (0.9–1.6)	Age, smoking, state, total days of any pesticide application	AHS [Strengths: large cohort. Limitations: based on self-reported exposure, limited to licensed applicators, potential
		Colon	Exposed to glyphosate	151			
		Rectum	Exposed to glyphosate	74			

Table 2.1 (continued)

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Andreotti *et al.* (2009) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up to 2004 Nested case–control study	Cases: 93 (response rate, NR); identified from population-based state-cancer registries. Incident cases diagnosed between enrolment and 31 December 2004 (> 9 years follow-up) included in the analysis. Participants with any type of prevalent cancer at enrolment were excluded. Vital status was obtained from the state death registries and the National Death Index. Participants who left North Carolina or Iowa were not subsequently followed for cancer occurrence. Controls: 82 503 (response rate, NR); cancer-free participants enrolled in the cohort Exposure assessment method: questionnaire providing detailed pesticide use, demographic and lifestyle information. Ever-use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) × (exposure intensity score)] of 13 pesticides was assessed	Pancreas (C25.0–C25.9)	Ever exposure to glyphosate	55	1.1 (0.6–1.7)	Age, smoking, diabetes	AHS [Strengths: large cohort. Limitations: based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]
			Low (< 185 days)	29			
			High (≥ 185 days)	19			
			Trend-test *P* value: 0.85				

AHS, Agricultural Health Study; NHL, non-Hodgkin lymphoma; NR, not reported

(De Roos *et al.*, 2005b). [The study had limited power for the analysis of multiple myeloma; there were missing data on covariates when multiple adjustments were done, limiting the interpretation of the findings.] A re-analysis of these data conducted by Sorahan (2015) confirmed that the excess risk of multiple myeloma was present only in the subset with no missing information (of 22 cases in the restricted data set). In a subsequent cross-sectional analysis of 678 male participants from the same cohort, Landgren *et al.* (2009) did not find an association between exposure to glyphosate and risk of monoclonal gammopathy of undetermined significance (MGUS), a premalignant plasma disorder that often precedes multiple myeloma (odds ratio, OR, 0.5; 95% CI, 0.2–1.0; 27 exposed cases).

Flower *et al.* (2004) reported the results of the analyses of risk of childhood cancer associated with pesticide application by parents in the AHS. The analyses for glyphosate were conducted among 17 357 children of Iowa pesticide applicators from the AHS. Parents provided data via questionnaires (1993–1997) and the cancer follow-up (retrospectively and prospectively) was done through the state cancer registries. Fifty incident childhood cancers were identified (1975–1998; age, 0–19 years). For all the children of the pesticide applicators, risk was increased for all childhood cancers combined, for all lymphomas combined, and for Hodgkin lymphoma, compared with the general population. The odds ratio for use of glyphosate and risk of childhood cancer was 0.61 (95% CI, 0.32–1.16; 13 exposed cases) for maternal use and 0.84 (95% CI, 0.35–2.34; 6 exposed cases) for paternal use. [The Working Group noted that this analysis had limited power to study a rare disease such as childhood cancer.]

Engel *et al.* (2005) reported on incidence of cancer of the breast among farmers' wives in the AHS cohort, which included 30 454 women with no history of cancer of the breast before enrolment in 1993–1997. Information on pesticide use and other factors was obtained at enrolment by self-administered questionnaire from the women and their husbands. A total of 309 incident cases of cancer of the breast were identified until 2000. There was no difference in incidence of cancer of the breast for women who reported ever applying pesticides compared with the general population. The relative risk for cancer of the breast among women who had personally used glyphosate was 0.9 (95% CI, 0.7–1.1; 82 cases) and 1.3 (95% CI, 0.8–1.9; 109 cases) among women who never used pesticides but whose husband had used glyphosate. [No information on duration of glyphosate use by the husband was presented.] Results for glyphosate were not further stratified by menopausal status.

Lee *et al.* (2007) investigated the relationship between exposure to agricultural pesticides and incidence of cancer of the colorectum in the AHS. A total of 56 813 pesticide applicators with no prior history of cancer of the colorectum were included in this analysis, and 305 incident cancers of the colorectum (colon, 212; rectum, 93) were diagnosed during the study period, 1993–2002. Most of the 50 pesticides studied were not associated with risk of cancer of the colorectum, and the relative risks with exposure to glyphosate were 1.2 (95% CI, 0.9–1.6), 1.0 (95% CI, 0.7–1.5), and 1.6 (95% CI, 0.9–2.9) for cancers of the colorectum, colon, and rectum, respectively.

Andreotti *et al.* (2009) examined associations between the use of pesticides and cancer of the pancreas using a case–control analysis nested in the AHS. This analysis included 93 incident cases of cancer of the pancreas (64 applicators, 29 spouses) and 82 503 cancer-free controls who completed the enrolment questionnaire. Ever-use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) × (exposure intensity score)] of 13 pesticides were assessed. Risk estimates were calculated controlling for age, smoking, and diabetes. The odds ratio for ever- versus never-exposure to glyphosate was

1.1 (95% CI, 0.6–1.7; 55 exposed cases), while the odds ratio for the highest category of level of intensity-weighted lifetime days was 1.2 (95% CI, 0.6–2.6; 19 exposed cases).

Dennis *et al.* (2010) reported that exposure to glyphosate was not associated with cutaneous melanoma within the AHS. [The authors did not report a risk estimate.]

2.2 Case–control studies on non-Hodgkin lymphoma, multiple myeloma, and leukaemia

2.2.1 Non-Hodgkin lymphoma

See Table 2.2

(a) *Case–control studies in the midwest USA*

Cantor *et al.* (1992) conducted a case–control study of incident non-Hodgkin lymphoma (NHL) among males in Iowa and Minnesota, USA (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). A total of 622 white men and 1245 population-based controls were interviewed in person. The association with farming occupation and specific agricultural exposures were evaluated. When compared with non-farmers, the odds ratios for NHL were 1.2 (95% CI, 1.0–1.5) for men who had ever farmed, and 1.1 (95% CI, 0.7–1.9; 26 exposed cases; adjusted for vital status, age, state, cigarette smoking status, family history of lymphohaematopoietic cancer, high-risk occupations, and high-risk exposures) for ever handling glyphosate. [There was low power to assess the risk of NHL associated with exposure to glyphosate. There was no adjustment for other pesticides. These data were included in the pooled analysis by De Roos *et al.* (2003).]

Brown *et al.* (1993) reported the results of a study to evaluate the association between multiple myeloma and agricultural risk factors in the midwest USA (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). A population-based case–control study of 173 white men with multiple myeloma and 650 controls was conducted in Iowa, USA, an area with a large farming population. A non-significantly elevated risk of multiple myeloma was seen among farmers compared with never-farmers. The odds ratio related to exposure to glyphosate was 1.7 (95% CI, 0.8–3.6; 11 exposed cases). [This study had limited power to assess the association between multiple myeloma and exposure to glyphosate. Multiple myeloma is now considered to be a subtype of NHL.]

De Roos *et al.* (2003) used pooled data from three case–control studies of NHL conducted in the 1980s in Nebraska (Zahm *et al.*, 1990), Kansas (Hoar *et al.*, 1986), and in Iowa and Minnesota (Cantor *et al.*, 1992) (see the *Monograph* on Malathion, Section 2.0, for a detailed description of these studies) to examine pesticide exposures in farming as risk factors for NHL in men. The study population included 870 cases and 2569 controls; 650 cases and 1933 controls were included for the analysis of 47 pesticides controlling for potential confounding by other pesticides. Both logistic regression and hierarchical regression (adjusted estimates were based on prior distributions for the pesticide effects, which provides more conservative estimates than logistic regression) were used in data analysis, and all models were essentially adjusted for age, study site, and other pesticides. Reported use of glyphosate as well as several individual pesticides was associated with increased incidence of NHL. Based on 36 cases exposed, the odds ratios for the association between exposure to glyphosate and NHL were 2.1 (95% CI, 1.1–4.0) in the logistic regression analyses and 1.6 (95% CI, 0.9–2.8) in the hierarchical regression analysis. [The numbers of cases and controls were lower than those in the pooled analysis by Waddell *et al.* (2001) because only subjects with no missing data on pesticides were included. The strengths of this study when compared with other studies are that it was large,

Table 2.2 Case–control studies of leukaemia and lymphoma and exposure to glyphosate

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
USA							
Brown *et al.* (1990) Iowa and Minnesota, USA 1981–1983	Cases: 578 (340 living, 238 deceased) (response rate, 86%); cancer registry or hospital records Controls: 1245 (820 living, 425 deceased) (response rate, 77–79%); random-digit dialling for those aged < 65 years and Medicare for those aged ≥ 65 years Exposure assessment method: questionnaire	Leukaemia	Any glyphosate	15	0.9 (0.5–1.6)	Age, vital status, state, tobacco use, family history lymphopoietic cancer, high-risk occupations, high risk exposures	[Strengths: large population based study in a farming area. Limitations: not controlled for exposure to other pesticides. Limited power for glyphosate exposure]
Cantor *et al.* (1992) Iowa and Minnesota, USA 1980–1982	Cases: 622 (response rate, 89.0%); Iowa health registry records and Minnesota hospital and pathology records Controls: 1245 (response rate, 76–79%); population-based; no cancer of the lympho-haematopoietic system; frequency-matched to cases by age (5-year group), vital status, state. Random-digit dialling (aged < 65 years); Medicare records (aged ≥ 65 years); state death certificate files (deceased subjects) Exposure assessment method: questionnaire; in-person interview	NHL	Ever handled glyphosate	26	1.1 (0.7–1.9)	Age, vital status, state, smoking status, family history lymphopoietic cancer, high-risk occupations, high-risk exposures	Data subsequentially pooled in De Roos *et al.* (2003); white men only [Strengths: large population-based study in farming areas. Limitations: not controlled for exposure to other pesticides. Limited power for glyphosate exposure]

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Brown et al. (1993) Iowa, USA 1981–1984	Cases: 173 (response rate, 84%); Iowa health registry Controls: 650 (response rate, 78%); Random-digit dialling (aged < 65 years) and Medicare (aged > 65 years) Exposure assessment method: questionnaire	Multiple myeloma	Any glyphosate	11	1.7 (0.8–3.6)	Age, vital status	[Strengths: population-based study. Areas with high prevalence of farming. Limitations: limited power for glyphosate exposure]
De Roos et al. (2003) Nebraska, Iowa, Minnesota, Kansas, USA 1979–1986	Cases: 650 (response rate, 74.7%); cancer registries and hospital records Controls: 1933 (response rate, 75.2%); random-digit dialling, Medicare, state mortality files Exposure assessment method: questionnaire, interview (direct or next-of-kin)	NHL	Any glyphosate exposure	36	2.1 (1.1–4)	Age, study area, other pesticides	Both logistic regression and hierarchical regression were used in data analysis, the latter providing more conservative estimates [Strengths: increased power when compared with other studies, population-based, and conducted in farming areas. Advanced analytical methods to account for multiple exposures] Included participants from Cantor et al. (1992), Zahm et al. (1990), Hoar et al. (1986), and Brown et al. (1990)

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lee et al. (2004a) Iowa, Minnesota and Nebraska, USA 1980–1986	Cases: 872 (response rate, NR); diagnosed with NHL from 1980 to 1986 Controls: 2381 (response rate, NR); frequency-matched controls Exposure assessment method: questionnaire; information on use of pesticides and history of asthma was based on interviews	NHL	Exposed to glyphosate – non-asthmatics	53	1.4 (0.98–2.1)	Age, vital status, state	177 participants (45 NHL cases, 132 controls) reported having been told by their doctor that they had asthma
			Exposed to glyphosate – asthmatics	6	1.2 (0.4–3.3)		
Canada							
McDuffie et al. (2001) Canada 1991–1994	Cases: 517 (response rate, 67.1%), from cancer registries and hospitals Controls: 1506 (response rate, 48%); random sample from health insurance and voting records Exposure assessment method: questionnaire, some administered by telephone, some by post	NHL	Exposed to glyphosate	51	1.2 (0.83–1.74)	Age, province of residence	Cross-Canada study [Strengths: large population based study. Limitations: no quantitative exposure data. Exposure assessment by questionnaire. Relatively low participation]
			Unexposed	464	1		
			> 0 and ≤ 2 days	28	1.0 (0.63–1.57)		
			> 2 days	23	2.12 (1.2–3.73)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Karunanayake et al. (2012) Six provinces in Canada (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia) 1991–1994	Incident cases: 316 (response rate, 68.4%); men aged ≥ 19 years; ascertained from provincial cancer registries, except in Quebec (hospital ascertainment) Controls: 1506 (response rate, 48%); matched by age ± 2 years to be comparable with the age distribution of the entire case group (HL, NHL, MM, and STS) within each province of residence. Potential controls (men aged ≥ 19 years) selected at random within age constraints from the provincial health insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario), or voters' lists (British Columbia) Exposure assessment method: questionnaire; stage 1 used a self-administered postal questionnaire, and in stage 2 detailed pesticide exposure information was collected by telephone interview	HL (ICDO2 included nodular sclerosis (M9656/3; M9663/3; M9664/3; M9665/3; M9666/3; M9667/3), lymphocytic predominance (M9651/3; M9657/3; M9658/3; M9659/3), mixed cellularity (M9652/3), lymphocytic depletion (M9653/3; M9654/3), miscellaneous (other M9650-M9669 codes for HL)	Glyphosate-based formulation	38	1.14 (0.74–1.76)	Age group, province of residence	Cross Canada study Based on the statistical analysis of pilot study data, it was decided that the most efficient definition of pesticide exposure was a cumulative exposure ≥ 10 hours/year to any combination of pesticides. This discriminated (a) between incidental, bystander, and environmental exposure vs more intensive exposure, and (b) between cases and controls [Strengths: large study. Limitations: low response rates]
			Glyphosate-based formulation	38	0.99 (0.62–1.56)	Age group, province of residence, medical history	

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kachuri *et al.* (2013) Six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario and Quebec) 1991–1994	Cases: 342 (response rate, 58%); men aged ≥ 19 years diagnosed between 1991 and 1994 were ascertained from provincial cancer registries except in Quebec, where ascertained from hospitals Controls: 1357 (response rate, 48%); men aged ≥ 19 years selected randomly using provincial health insurance records, random digit dialling, or voters' lists, frequency-matched to cases by age (±2 years) and province of residence Exposure assessment method: questionnaire	Multiple myeloma	Glyphosate use	32	1.19 (0.76–1.87)	Age, province of residence, use of a proxy respondent, smoking status, medical variables, family history of cancer	Cross-Canada study [Strengths: population-based case–control study. Limitations: relatively low response rates]
			Use of glyphosate (> 0 and ≤ 2 days per year)	15	0.72 (0.39–1.32)		
			Use of glyphosate (> 2 days per year)	12	2.04 (0.98–4.23)		
Sweden							
Nordström *et al.* (1998) Sweden 1987–1992	Cases: 111 (response rate, 91%); 121 HCL cases in men identified from Swedish cancer registry Controls: 400 (response rate, 83%); 484 (four controls/case) matched for age and county; national population registry Exposure assessment method: questionnaire; considered exposed if minimum exposure of 1 working day (8 h) and an induction period of at least 1 year	HCL	Exposed to glyphosate	4	3.1 (0.8–12)	Age	Overlaps with Hardell *et al.* (2002). HCL is a subtype of NHL [Strengths: population-based case–control study. Limitations: Limited power. There was no adjustment for other exposures]

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hardell & Eriksson (1999) Northern and middle Sweden 1987–1990	Cases: 404 (192 deceased) (response rate, 91%); regional cancer registries Controls: 741 (response rate, 84%); live controls matched for age and county were recruited from the national population registry, and deceased cases matched for age and year of death were identified from the national registry for causes of death Exposure assessment method: questionnaire	NHL (ICD-9 200 and 202)	Ever glyphosate – univariate	4	2.3 (0.4–13)	Not specified in the multivariable analysis	Overlaps with Hardell et al. (2002) [Strengths: population-based study. Limitations: few subjects were exposed to glyphosate and the study had limited power. Analyses were "multivariate" but covariates were not specified]
			Ever glyphosate – multivariate	NR	5.8 (0.6–54)		
Hardell et al. (2002) Sweden; four Northern counties and three counties in mid Sweden 1987–1992	Cases: 515 (response rate, 91% in both studies); Swedish cancer registry Controls: 1141 (response rates, 84% and 83%%); national population registry Exposure assessment method: questionnaire	NHL and HCL	Ever glyphosate exposure (univariate)	8	3.04 (1.08–8.5)	Age, county, study site, vital status, other pesticides in the multivariate analysis	Overlaps with Nordström et al. (1998) and Hardell & Eriksson (1999), [Strengths: large population-based study. Limitations: limited power for glyphosate exposure]
			Ever glyphosate exposure (multivariate)	8	1.85 (0.55–6.2)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Eriksson et al. (2008) Sweden. Four health service areas (Lund, Linkoping, Orebro and Umea) 1999–2002	Cases: 910 (response rate, 91%); incident NHL cases were enrolled from university hospitals Controls: 1016 (response rate, 92%); national population registry Exposure assessment method: questionnaire	NHL	Any glyphosate	29	2.02 (1.1–3.71)	Age, sex, year of enrolment	[Strengths: population-based case-control. Limitations: limited power for glyphosate] * Exposure to other pesticides (e.g. MPCA) controlled in the analysis
			Any glyphosate*	29	1.51 (0.77–2.94)		
			≤ 10 days per year use	12	1.69 (0.7–4.07)		
			> 10 days per year use	17	2.36 (1.04–5.37)		
		NHL	1–10 yrs	NR	1.11 (0.24–5.08)		
			> 10 yrs	NR	2.26 (1.16–4.4)		
		B-cell lymphoma	Exposure to glyphosate	NR	1.87 (0.998–3.51)		
		Lymphocytic lymphoma/B-CLL	Exposure to glyphosate	NR	3.35 (1.42–7.89)		
		Diffuse large B-cell lymphoma	Exposure to glyphosate	NR	1.22 (0.44–3.35)		
		Follicular, grade I–III	Exposure to glyphosate	NR	1.89 (0.62–5.79)		
		Other specified B-cell lymphoma	Exposure to glyphosate	NR	1.63 (0.53–4.96)		
		Unspecified B-cell lymphoma	Exposure to glyphosate	NR	1.47 (0.33–6.61)		
		T-cell lymphoma	Exposure to glyphosate	NR	2.29 (0.51–10.4)		
		Unspecified NHL	Exposure to glyphosate	NR	5.63 (1.44–22)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Other studies in Europe							
Orsi *et al.* (2009) France 2000–2004	Cases: 491 (response rate, 95.7%); cases (244 NHL; 87 HL; 104 LPSs; 56 MM) were recruited from main hospitals of the French cities of Brest, Caen, Nantes, Lille, Toulouse and Bordeaux, aged 20–75 years; ALL cases excluded Controls: 456 (response rate, 91.2%); matched on age and sex, recruited in the same hospitals as the cases, mainly in orthopaedic and rheumatological departments and residing in the hospital's catchment area Exposure assessment method: questionnaire	NHL	Any glyphosate exposure	12	1.0 (0.5–2.2)	Age, centre, socioeconomic category (blue/ white collar)	[Limitations: limited power for glyphosate]
		HL	Any exposure to glyphosate	6	1.7 (0.6–5)		
		LPS	Any exposure to glyphosate	4	0.6 (0.2–2.1)		
		MM	Any exposure to glyphosate	5	2.4 (0.8–7.3)		
		All lymphoid neoplasms	Any exposure to glyphosate	27	1.2 (0.6–2.1)		
		NHL, diffuse large cell lymphoma	Occupational use of glyphosate	5	1.0 (0.3–2.7)		
		NHL, follicular lymphoma	Occupational exposure to glyphosate	3	1.4 (0.4–5.2)		
		LPS/CLL	Occupational exposure to glyphosate	2	0.4 (0.1–1.8)		
		LPS/HCL	Occupational exposure to glyphosate	2	1.8 (0.3–9.3)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cocco et al. (2013) Czech Republic, France, Germany, Italy, Ireland and Spain 1998–2004	Cases: 2348 (response rate, 88%); cases were all consecutive adult patients first diagnosed with lymphoma during the study period, resident in the referral area of the participating centres Controls: 2462 (response rate, 81% hospital; 52% population); controls from Germany and Italy were randomly selected by sampling from the general population and matched to cases on sex, 5-year age-group, and residence area. The rest of the centres used matched hospital controls, excluding diagnoses of cancer, infectious diseases and immunodeficiency diseases Exposure assessment method: questionnaire; support of a crop-exposure matrix to supplement the available information, industrial hygienists and occupational experts in each participating centre reviewed the general questionnaires and job modules to assess exposure to pesticides	B-cell lymphoma	Occupational exposure to glyphosate	4	3.1 (0.6–17.1)	Age, sex, education, centre	EPILYMPH case-control study in six European countries

ALL, acute lymphocytic leukaemia; B-CLL, chronic lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; HCL, hairy cell leukaemia; HL, Hodgkin lymphoma; LPS, lymphoproliferative syndrome; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; ref., reference; STS, soft tissue sarcoma population-based, and conducted in farming areas. Potential confounding from multiple exposures was accounted for in the analysis.]

Using the data set of the pooled population-based case–control studies in Iowa, Minnesota, and Nebraska, USA, Lee *et al.* (2004a) investigated whether asthma acts as an effect modifier of the association between pesticide exposure and NHL. The study included 872 cases diagnosed with NHL from 1980 to 1986 and 2381 frequency-matched controls. Information on use of pesticides and history of asthma was based on interviews. A total of 177 subjects (45 cases, 132 controls) reported having been told by their doctor that they had asthma. Subjects with a history of asthma had a non-significantly lower risk of NHL than non-asthmatics, and there was no main effect of pesticide exposure. In general, asthmatics tended to have larger odds ratios associated with exposure to pesticides than non-asthmatics. There was no indication of effect modification: the odds ratio associated with glyphosate use was 1.4 (95% CI, 0.98–2.1; 53 exposed cases) among non-asthmatics and 1.2 (95% CI, 0.4–3.3; 6 exposed cases) for asthmatics, when compared with non-asthmatic non-exposed farmers). [This analysis overlapped with that of De Roos *et al.* (2003).]

(b) The cross-Canada case–control study

McDuffie *et al.* (2001) studied the associations between exposure to specific pesticides and NHL in a multicentre population-based study with 517 cases and 1506 controls among men of six Canadian provinces (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). Odds ratios of 1.26 (95% CI, 0.87–1.80; 51 exposed cases; adjusted for age and province) and 1.20 (95% CI, 0.83–1.74, adjusted for age, province, high-risk exposures) were observed for exposure to glyphosate. In an analysis by frequency of exposure to glyphosate, participants with > 2 days of exposure per year had an odds ratio of 2.12 (95% CI, 1.20–3.73, 23 exposed cases) compared with those with some, but ≤ 2 days of exposure. [The study was large, but had relatively low participation rates.]

Kachuri *et al.* (2013) investigated the association between lifetime use of pesticides and multiple myeloma in a population-based case–control study among men in six Canadian provinces between 1991 and 1994 (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). Data from 342 cases of multiple myeloma and 1357 controls were obtained for ever-use of pesticides, number of pesticides used, and days per year of pesticide use. The odds ratios were adjusted for age, province of residence, type of respondent, smoking and medical history. The odds ratio for ever-use of glyphosate was 1.19 (95% CI, 0.76–1.87; 32 cases). When the analysis was conducted by level of exposure, no association was found for light users (≤ 2 days per year) of glyphosate (OR, 0.72; 95% CI, 0.39–1.32; 15 exposed cases) while the odds ratio in heavier users (> 2 days per year) was 2.04 (95% CI, 0.98–4.23; 12 exposed cases). [The study had relatively low response rates. Multiple myeloma is now considered a subtype of NHL.]

(c) Case–control studies in Sweden

Nordström *et al.* (1998) conducted a population case–control study in Sweden on hairy cell leukaemia (considered to be a subgroup of NHL). The study included 121 cases in men and 484 controls matched for age and sex. An age-adjusted odds ratio of 3.1 (95% CI, 0.8–12; 4 exposed cases) was observed for exposure to glyphosate. [This study had limited power to detect an effect, and there was no adjustment for other exposures.]

Hardell & Eriksson (1999) reported the results of a population-based case–control study on the incidence of NHL in men associated with pesticide exposure in four northern counties in Sweden. Exposure data was collected by questionnaire (also supplemented by telephone interviews) from 404 cases (192 deceased) and 741 controls (matched by age, sex, county, and vital status). Increased risks of NHL were found for subjects exposed to herbicides and fungicides. The odds ratio for ever-use of glyphosate was 2.3 (95% CI, 0.4–13; 4 exposed cases) in a univariate analysis, and 5.8 (95% CI, 0.6–54) in a multivariable analysis. [The exposure frequency was low for glyphosate, and the study had limited power to detect an effect. The variables included in the multivariate analysis were not specified. This study may have overlapped partially with those of Hardell *et al.* (2002).]

Hardell *et al.* (2002) conducted a pooled analysis of two case–control studies, one on NHL (already reported in Hardell & Eriksson, 1999) and another on hairy cell leukaemia, a subtype of NHL (already reported by Nordström *et al.*, 1998). The pooled analysis of NHL and hairy cell leukaemia was based on 515 cases and 1141 controls. Increased risk was found for exposure to glyphosate (OR, 3.04; 95% CI, 1.08–8.52; 8 exposed cases) in the univariate analysis, but the odds ratio decreased to 1.85 (95% CI, 0.55–6.20) when study, study area, and vital status were considered in a multivariate analysis. [The exposure frequency was low for glyphosate and the study had limited power. This study partially overlapped with those of Hardell & Eriksson (1999) and Nordström *et al.* (1998).]

Eriksson *et al.* (2008) reported the results of a population based case–control study of exposure to pesticides as a risk factor for NHL. Men and women aged 18–74 years living in Sweden were included from 1 December 1999 to 30 April 2002. Incident cases of NHL were enrolled from university hospitals in Lund, Linköping, Örebro, and Umeå. Controls (matched by age and sex) were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total, 910 (91%) cases and 1016 (92%) controls participated. Multivariable models included agents with statistically significant increased odds ratios (MCPA, 2-methyl-4-chlorophenoxyacetic acid), or with an odds ratio of > 1.50 and at least 10 exposed subjects (2,4,5-T and/or 2,4-D; mercurial seed dressing, arsenic, creosote, tar), age, sex, year of diagnosis or enrolment. The odds ratio for exposure to glyphosate was 2.02 (95% CI, 1.10–3.71) in a univariate analysis, and 1.51 (95% CI, 0.77–2.94) in a multivariable analysis. When exposure for more than 10 days per year was considered, the odds ratio was 2.36 (95% CI, 1.04–5.37). With a latency period of > 10 years, the odds ratio was 2.26 (95% CI, 1.16–4.40). The associations with exposure to glyphosate were reported also for lymphoma subtypes, and elevated odds ratios were reported for most of the cancer forms, including B-cell lymphoma (OR, 1.87; 95% CI, 0.998–3.51) and the subcategory of small lymphocytic lymphoma/chronic lymphocytic leukaemia (OR, 3.35; 95% CI, 1.42–7.89; [not adjusted for other pesticides]). [This was a large study; there was possible confounding from use of other pesticides including MCPA, but this was considered in the analysis.]

(d) *Other case–control studies in Europe*

Orsi *et al.* (2009) reported the results of a hospital-based case–control study conducted in six centres in France between 2000 and 2004. Incident cases with a diagnosis of lymphoid neoplasm aged 20–75 years and controls of the same age and sex as the cases were recruited in the same hospital, mainly in the orthopaedic and rheumatological departments during the same period. [The Working Group noted that the age of case eligibility was given in the publication as 20–75 years in the materials and methods section, but as 18–75 years in the abstract.] Exposures to pesticides were evaluated through specific interviews and case-by-case expert reviews. The analyses included 491 cases (244 cases of NHL, 87 cases of Hodgkin lymphoma), 104 of lymphoproliferative syndrome, and 56 cases of multiple myeloma), and 456 age- and sex-matched controls. Positive associations between some subtypes and occupational exposure to several pesticides were noted. The odds ratios associated with any exposure to glyphosate were 1.2 (95% CI, 0.6–2.1; 27 exposed cases) for all lymphoid neoplasms combined, 1.0 (95% CI, 0.5–2.2; 12 exposed cases) for NHL, 0.6 (95% CI, 0.2–2.1; 4 exposed cases) for lymphoproliferative syndrome, 2.4 (95% CI, 0.8–7.3) for multiple myeloma, and 1.7 (95% CI, 0.6–5.0; 6 exposed cases) for Hodgkin lymphoma, after adjusting for age, centre, and socioeconomic category ("blue/white collar").

Cocco *et al.* (2013) reported the results of a pooled analysis of case–control studies conducted in six European countries in 1998–2004 (EPILYMPH, Czech Republic, France, Germany, Ireland, Italy, and Spain) to investigate the role of occupational exposure to specific groups of chemicals in the etiology of lymphoma overall, B-cell lymphoma, and its most prevalent subtypes. A total of 2348 incident cases of lymphoma and 2462 controls were recruited. Controls from Germany and Italy were randomly selected by sampling from the general population, while the rest of the centres used matched hospital controls. Overall, the participation rate was 88% for cases, 81% for hospital controls, and 52% for population controls. An occupational history was collected with farm work-specific questions on type of crop, farm size, pests being treated, type and schedule of pesticide use. In each study centre, industrial hygienists and occupational experts assessed exposure to specific groups of pesticides and individual compounds with the aid of agronomists. [Therefore any exposure misclassification would be non-differential.] Analyses were conducted for lymphoma and the most prevalent lymphoma subtypes adjusting for age, sex, education, and centre. Lymphoma overall, and B-cell lymphoma were not associated with any class of the investigated pesticides, while the risk of chronic lymphocytic leukaemia was elevated among those ever exposed to inorganic and organic pesticides. Only for a few individual agrochemicals was there a sizeable number of study subjects to conduct a meaningful analysis, and the odds ratio for exposure to glyphosate and B-cell lymphoma was 3.1 (95% CI, 0.6–17.1; 4 exposed cases and 2 exposed controls). [The study had a very limited power to assess the effects of glyphosate on risk of NHL.]

2.2.2 *Other haematopoietic cancers*

Orsi *et al.* (2009) also reported results for Hodgkin lymphoma (see Section 2.2.1).

Karunanayake *et al.* (2012) conducted a case–control study of Hodgkin lymphoma among white men, aged 19 years or older, in six regions of Canada (see the Malathion *Monograph*, Section 2.0, for a detailed description of this study). The analysis included 316 cases and 1506 age-matched (± 2 years) controls. Based on 38 cases exposed to glyphosate, the odds ratios were 1.14 (95% CI, 0.74–1.76) adjusted for age and province, and 0.99 (95% CI, 0.62–1.56) when additionally adjusted for medical history variables.

Brown *et al.* (1990) evaluated exposure to carcinogens in an agricultural setting and the relationship with leukaemia in a population-based case–control interview study in Iowa and Minnesota, USA, including 578 white men with leukaemia and 1245 controls. The exposure assessment was done with a personal interview of the living subjects or the next-of-kin. Farmers had a higher risk of all leukaemias compared with non-farmers, and associations were found for exposure to specific animal insecticides, including the organophosphates crotoxyphos, dichlorvos, famphur, pyrethrins, and methoxychlor. The odds ratio for glyphosate was 0.9 (95% CI, 0.5–1.6; 15 exposed cases; adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures). [This was a large study in an agricultural setting, but had limited power for studying the effects of glyphosate use.]

2.3 Case–control studies on other cancer sites

2.3.1 Cancer of the oesophagus and stomach

Lee *et al.* (2004b) evaluated the risk of adenocarcinomas of the oesophagus and stomach associated with farming and agricultural pesticide use. The population-based case–control study was conducted in eastern Nebraska, USA. Subjects of both sexes diagnosed with adenocarcinoma of the stomach ($n = 170$) or oesophagus ($n = 137$) between 1988 and 1993 were enrolled. Controls ($n = 502$) were randomly selected from the population registry of the same geographical area. The response rates were 79% for cancer of the stomach, 88% for cancer of the oesophagus, and 83% for controls. Adjusted odds ratios were estimated for use of individual and chemical classes of insecticides and herbicides, with non-farmers as the reference category. No association was found with farming or ever-use of insecticides or herbicides, or with individual pesticides. For ever-use of glyphosate, the odds ratio was 0.8 (95% CI, 0.4–1.4; 12 exposed cases) for cancer of the stomach, and 0.7 (95% CI, 0.3–1.4; 12 exposed cases) for oesophageal cancer. [The study was conducted in a farming area, but the power to detect an effect of glyphosate use was limited.]

2.3.2 Cancer of the brain

Ruder *et al.* (2004) conducted a case–control study on glioma among nonmetropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin in the Upper Midwest Health Study, USA. The study included 457 cases of glioma and 648 population-based controls, all adult men. Exposure assessment was done with interviews of the subject or the relatives. The response rates were 93% and 70% for cases and controls, respectively. No association were found with any of the pesticides assessed, including glyphosate. [Glyphosate use was assessed, but specific results were not presented.]

Carreón *et al.* (2005) evaluated the effects of rural exposures to pesticides on risk of glioma among women aged 18–80 years who were nonmetropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin in the Upper Midwest Health Study, USA. A total of 341 cases of glioma and 528 controls were enrolled. A personal interview was carried out for exposure assessment. The response rates were 90% and 72%, respectively. After adjusting for age, age group, education, and farm residence, no association with glioma was observed for exposure to several pesticide classes or individual pesticides. There was a reduced risk for glyphosate (OR, 0.7; 95% CI, 0.4–1.3; 18 exposed cases). These results were not affected by the exclusion of proxy respondents (43% of cases, 2% of controls).

Lee *et al.* (2005) evaluated the association between farming and agricultural pesticide use and risk of adult glioma in a population-based case–control study in eastern Nebraska, USA. Cases of glioma were in men and women ($n = 251$) and were compared with population controls from a previous study ($n = 498$). A telephone interview was conducted for 89% of the cases and 83% of the controls. Adjusted odds ratios for farming and for use of individual and chemical classes of insecticides and herbicides were calculated using non-farmers as the reference category. Among men, ever living or working on a farm and duration of farming were associated with significantly increased risks of glioma, but the positive findings were limited to proxy respondents. Among women, there were no positive associations with farming activities among self or proxy respondents. Some specific pesticide families and individual pesticides were associated with significantly increased risks among male farmers, but most of the positive associations were limited to proxy respondents. There was a non-significant excess risk with glyphosate use for the overall group (OR, 1.5; 95% CI, 0.7–3.1; 17 exposed cases), but there was inconsistency between observations for self-respondents (OR, 0.4; 95% CI, 0.1–1.6) and observations for proxy respondents (OR, 3.1; 95% CI, 1.2–8.2). [The study had limited power to detect an effect of glyphosate use, and the inconsistencies for self and proxy respondents made the results difficult to interpret.]

2.3.3 Soft tissue sarcoma

Pahwa *et al.* (2011) reported the results of the soft tissue sarcoma component of the cross-Canada study in relation to specific pesticides, including 357 cases of soft tissue sarcoma and 1506 population controls from 1991–1994. The fully adjusted odds ratio for glyphosate use was 0.90 (95% CI, 0.58–1.40).

2.3.4 Cancer of the prostate

Band *et al.* (2011) report results of a case–control study including 1516 patients with cancer of the prostate (ascertained by the cancer registry of British Columbia, Canada, for 1983–90) and 4994 age-matched controls with cancers at all other cancer sites excluding lung and unknown primary site. Agricultural exposures were assessed by job-exposure matrix. A total of 60 cases were exposed to glyphosate (adjusted OR, 1.36; 95% CI, 0.83–2.25).

2.3.5 Childhood cancer

Parental exposure to pesticides, including glyphosate, was assessed in a population-based case–control study of childhood leukaemia in Costa Rica (Monge *et al.*, 2007). However, associations of childhood cancer with glyphosate were reported only for an "other pesticides" category that also included paraquat, chlorothalonil, and other chemicals. [Because glyphosate was not specifically assessed, this study was not evaluated by the Working Group.]

2.4. Meta-analyses

Schinasi & Leon (2014) conducted a systematic review and meta-analysis of NHL and occupational exposure to agricultural pesticides, including glyphosate. The meta-analysis for glyphosate included six studies (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; De Roos *et al.*, 2003; 2005a; Eriksson *et al.*, 2008; Orsi *et al.*, 2009) and yielded a meta risk-ratio of 1.5 (95% CI, 1.1–2.0). [The Working Group noted that the most fully adjusted risk estimates from the articles by Hardell *et al.* (2002) and Eriksson *et al.* (2008) were not used in this analysis. After considering the adjusted estimates of the two Swedish studies in the meta-analysis, the Working Group estimated a meta risk-ratio of 1.3 (95% CI, 1.03–1.65), I^2 = 0%, *P* for heterogeneity 0.589.]

3. Cancer in Experimental Animals

3.1 Mouse

See Table 3.1

3.1.1 Dietary administration

Groups of 50 male and 50 female CD-1 mice [age not reported] were given diets containing glyphosate (purity, 99.7%) at a concentration of 0, 1000, 5000, or 30 000 ppm, ad libitum, for 24 months. There was no treatment-related effect on body weight in male and female mice at the lowest or intermediate dose. There was a consistent decrease in body weight in the male and female mice at the highest dose compared with controls. Survival in all dose groups was similar to that of controls. There was a positive trend (*P* = 0.016, trend test; see EPA, 1985b) in the incidence of renal tubule adenoma in dosed male mice: 0/49, 0/49, 1/50 (2%), 3/50 (6%). [The Working Group noted that renal tubule adenoma is a rare tumour in CD-1 mice.] No data on tumours of the kidney

Table 3.1 Studies of carcinogenicity with glyphosate in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, CD-1 (M, F) 24 mo EPA (1985a, b, 1986, 1991a)	Diet containing glyphosate (technical grade; purity, 99.7%) at concentrations of 0, 1000, 5000, or 30 000 ppm, ad libitum, for 24 mo 50 M and 50 F/group [age, NR]	*Males* Renal tubule adenoma: 0/49, 0/49, 1/50 (2%), 3/50 (6%) *Females* No data provided on the kidney	*P* for trend = 0.016; see Comments	No information was provided on renal tubule adenomas in female mice, or on statistical analyses of tumour data EPA recommended that additional renal sections be cut and evaluated from all control and treated male mice. The pathology report for these additional sections (EPA, 1985b) showed the same incidence of renal tubule adenomas as originally reported, with no significant difference in incidence when comparing control and treated groups; however, the test for linear trend in proportions resulted in *P* = 0.016 EPA (1986) convened a PWG and requested additional pathological and statistical information on kidney tumours observed in male mice treated with glyphosate
		Report from the PWG of the EPA (1986): *Males* Renal tubule adenoma: 1/49 (2%), 0/49, 0/50, 1/50 (2%) Renal tubule carcinoma: 0/49, 0/49, 1/50 (2%), 2/50 (4%) Renal tubule adenoma or carcinoma (combined): 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%)	[NS] [*P* = 0.037; Cochran–Armitage trend test] [*P* = 0.034; Cochran–Armitage trend test]	
Mouse, CD-1 (M, F) 104 wk JMPR (2006)	Diet containing glyphosate (purity, 98.6%) at doses of 0, 100, 300, 1000 mg/kg bw, ad libitum, for 104 wk 50 M and 50 F/group [age, NR]	*Males* Haemangiosarcoma: 0/50, 0/50, 0/50, 4/50 (8%) Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue: 0/50, 2/50 (4%), 0/50, 2/50 (4%) *Females* Haemangiosarcoma: 0/50, 2/50 (4%), 0/50, 1/50 (2%) Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue: 0/50, 3/50 (6%), 3/50 (6%), 1/50 (2%)	[*P* < 0.001; Cochran–Armitage trend test] NS NS NS	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, Swiss (M) 32 wk George et al. (2010)	Initiation–promotion study Skin application of glyphosate-based formulation (glyphosate, 41%; POEA, ~15%) (referred to as "glyphosate") dissolved in 50% ethanol; DMBA dissolved in 50% ethanol, and TPA dissolved in 50% acetone, used in the groups described below 20 M/group	Skin tumours [called "papillomas" by the authors, following gross examination only]		Short duration of treatment, no solvent controls, and lack of any histopathological evaluation Age at start, NR (mice weighed 12–15 g bw) [The Working Group concluded this was an inadequate study for the evaluation of glyphosate]
	Group I: untreated control (no treatment)	Group I: 0/20		
	Group II: glyphosate only: 25 mg/kg bw topically, 3 × /wk, for 32 wk	Group II: 0/20		
	Group III: single topical application of DMBA, 52 µg/mouse, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group III: 20/20*, 7.8 ± 1.1	*$P < 0.05$ vs groups VI and VII	
	Group IV: single topical application of glyphosate, 25 mg/kg bw, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group I: 0/20		
	Group V: 3 × /wk topical application of glyphosate, 25 mg/kg bw, for 3 wk, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group V: 0/20		
	Group VI: single topical application of DMBA, 52 µg/mouse	Group VI: 0/20		
	Group VII: topical application of TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group VII: 0/20		
	Group VIII: single topical application of DMBA, 52 µg/mouse, followed 1 wk later by topical treatment with glyphosate, 25 mg/kg bw, 3 × /wk, for 32 wk	Group VIII: 8/20*, 2.8 ± 0.9	*$P < 0.05$ vs group VI	

bw, body weight; DMBA, 7,12-dimethylbenz[a]anthracene; EPA, United States Environmental Protection Agency; F, female; M, male; mo, month; NR, not reported; NS, not significant; POEA, polyethoxylated tallowamine; PWG, pathology working group; TPA, 12-O-tetradecanoyl-phorbol-13-acetate; vs, versus; wk, week; yr, year were provided for female mice. No other tumour sites were identified (EPA, 1985a). Subsequent to its initial report (EPA, 1985a), the United States Environmental Protection Agency (EPA) recommended that additional renal sections be cut and evaluated from all male mice in the control and treated groups. The pathology report for these additional sections (EPA, 1985b) indicated the same incidence of renal tubule adenoma as originally reported, with no significant increase in incidence between the control group and treated groups by pairwise comparison. However, as already reported above, the test for linear trend in proportions resulted in a significance of $P = 0.016$. The EPA (1986) also requested that a pathology working group (PWG) be convened to evaluate the tumours of the kidney observed in male mice treated with glyphosate, including the additional renal sections. In this second evaluation, the PWG reported that the incidence of adenoma of the renal tubule was 1/49 (2%), 0/49, 0/50, 1/50 (2%) [not statistically significant]; the incidence of carcinoma of the renal tubule was 0/49, 0/49, 1/50 (2%), 2/50 (4%) [$P = 0.037$, trend test for carcinoma]; and the incidence of adenoma or carcinoma (combined) of the renal tubule was 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%) [$P = 0.034$, trend test for combined]. [The Working Group considered that this second evaluation indicated a significant increase in the incidence of rare tumours, with a dose-related trend, which could be attributed to glyphosate. Chandra & Frith (1994) reported that only 1 out of 725 [0.14%] CD-1 male mice in their historical database had developed renal cell tumours (one carcinoma).]

[The Working Group noted the differences in histopathological diagnosis between pathologists. Proliferative lesions of the renal tubules are typically categorized according to published criteria as hyperplasia, adenoma, or carcinoma. The difference is not trivial, because focal hyperplasia, a potentially preneoplastic lesion, should be carefully differentiated from the regenerative changes of the tubular epithelium. There is a morphological continuum in the development and progression of renal neoplasia. Thus larger masses may exhibit greater heterogeneity in histological growth pattern, and cytologically more pleomorphism and atypia than smaller lesions (Eustis *et al.*, 1994). Of note, a renal tumour confirmed by the PWG after re-evaluation of the original slides (EPA, 1986), had not been seen in the re-sectioned kidney slides (EPA, 1985b). This may be related to the growth of tumour that – in contrast to tumours in other organs – is not spherical but elliptical because of the potential expansion in tubules. In addition, the concept of tubular expansion without compression of adjacent parenchyma may be at the basis of the discrepancy between the first (EPA, 1985a, b) and second evaluation (EPA, 1986).]

In another study reported to the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), groups of 50 male and 50 female CD-1 mice [age at start not reported] were given diets containing glyphosate (purity, 98.6%) at a concentration that was adjusted weekly for the first 13 weeks and every 4 weeks thereafter to give doses of 0, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 weeks (JMPR, 2006). There was no treatment-related effect on body weight or survival in any of the dosed groups. There was an increase in the incidence of haemangiosarcoma in males – 0/50, 0/50, 0/50, 4/50 (8%) [$P < 0.001$, Cochran–Armitage trend test], and in females – 0/50, 2/50 (4%), 0/50, 1/50 (2%) [not statistically significant], and an increase in the incidence of histiocytic sarcoma in the lymphoreticular/haemopoietic tissue in males – 0/50, 2/50 (4%), 0/50, 2/50 (4%), and in females – 0/50, 3/50 (6%), 3/50 (6%), 1/50 (2%) [not statistically significant for males or females]. [The Working Group considered that this study was adequately reported.]

3.1.2 Initiation–promotion

Groups of 20 male Swiss mice [age at start not reported; body weight, 12–15 g] were given a glyphosate-based formulation (glyphosate, 41%; polyethoxylated tallowamine, ~15%) (referred to as glyphosate in the article) that was dissolved in 50% ethanol and applied onto the shaved back skin (George *et al.*, 2010). Treatment groups were identified as follows:

- Group I – untreated control;
- Group II – glyphosate only (25 mg/kg bw), applied topically three times per week for 32 weeks;
- Group III – single topical application of dimethylbenz[*a*]anthracene (DMBA; in ethanol; 52 µg/mouse), followed 1 week later by 12-*O*-tetradecanoylphorbol-13-acetate (TPA; in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group IV – single topical application of glyphosate (25 mg/kg bw) followed 1 week later by TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group V – glyphosate (25 mg/kg bw) applied topically three times per week for 3 weeks (total of nine applications), followed 1 week later by TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group VI – single topical application of DMBA (in ethanol; 52 µg/mouse);
- Group VII – TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks; and
- Group VIII – single topical application of DMBA (in ethanol; 52 µg/mouse), followed 1 week later by glyphosate (25 mg/kg bw), applied topically three times per week for 32 weeks.

All mice were killed at 32 weeks. Skin tumours were observed only in group III (positive control, DMBA + TPA, 20/20) and group VIII (DMBA + glyphosate, 8/20; $P < 0.05$ versus group VI [DMBA only, 0/20]). No microscopic examination was conducted and tumours were observed "as a minute wart like growth [that the authors called squamous cell papillomas], which progressed during the course of experiment." [The glyphosate formulation tested appeared to be a tumour promoter in this study. The design of the study was poor, with short duration of treatment, no solvent controls, small number of animals, and lack of histopathological examination. The Working Group concluded that this was an inadequate study for the evaluation of glyphosate.]

3.1.3 Review articles

Greim *et al.* (2015) have published a review article containing information on five long-term bioassay feeding studies in mice. Of these studies, one had been submitted for review to the EPA (EPA, 1985a, b, 1986, 1991a), and one to the JMPR (JMPR, 2006); these studies are discussed in Section 3.1.1. The review article reported on an additional three long-term bioassay studies in mice that had not been previously available in the open literature, but had been submitted to various organizations for registration purposes. The review article provided a brief summary of each study and referred to an online data supplement containing the original data on tumour incidence from study reports. The three additional long-term bioassay studies in mice are summarized below. [The Working Group was unable to evaluate these studies, which are not included in Table 3.1 and Section 5.3, because the information provided in the review article and its supplement was insufficient (e.g. information was lacking on statistical methods, choice of doses, body-weight gain, survival data, details of histopathological examination, and/or stability of dosed feed mixture).]

In the first study (identified as Study 12, 1997a), groups of 50 male and 50 female CD-1 mice [age at start not reported] were given diets containing glyphosate (purity, 94–96%) at a concentration of 0, 1600, 8000, or 40 000 ppm for 18 months. The increase in the incidence of bronchiolo-alveolar adenoma and carcinoma, and of lymphoma, was reported to be not statistically significant in males and females receiving glyphosate. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In the second study (identified as Study 13, 2001), groups of 50 male and 50 female Swiss albino mice [age at start not reported] were given diets containing glyphosate (purity, > 95%) at a concentration of 0 (control), 100, 1000, or 10 000 ppm for 18 months. The authors reported a statistically significant increase in the incidence of malignant lymphoma (not otherwise specified, NOS) in males at the highest dose: 10/50 (20%), 15/50 (30%), 16/50 (32%), 19/50 (38%; $P < 0.05$; pairwise test); and in females at the highest dose: 18/50 (36%), 20/50 (40%), 19/50 (38%), 25/50 (50%; $P < 0.05$; pairwise test). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In the third study (identified as Study 14, 2009a), groups of 51 male and 51 female CD-1 mice [age at start not reported] were given diets containing glyphosate (purity, 94.6–97.6%) at a concentration of 0, 500, 1500, or 5000 ppm for 18 months. Incidences for bronchiolo-alveolar adenoma and carcinoma, malignant lymphoma (NOS), and hepatocellular adenoma and carcinoma in males, and for bronchiolo-alveolar adenoma and carcinoma, malignant lymphoma (NOS) and pituitary adenoma in females, were included in the article. In males, the authors reported that there was a significant positive trend [statistical test not specified] in the incidence of bronchiolo-alveolar carcinoma (5/51, 5/51, 7/51, 11/51) and of malignant lymphoma (0/51, 1/51, 2/51, 5/51). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

3.2 Rat

See Table 3.2

3.2.1 Drinking-water

Groups of 10 male and 10 female Sprague-Dawley rats (age, 5 weeks) were given drinking-water containing a glyphosate-based formulation at a dose of 0 (control), $1.1 \times 10^{-8}\%$ (5.0×10^{-5} mg/L), 0.09% (400 mg/L) or 0.5% (2.25×10^{3} mg/L), ad libitum, for 24 months (Séralini *et al.*, 2014). [The study reported is a life-long toxicology study on a glyphosate-based formulation and on genetically modified NK603 maize, which the authors stated was designed as a full study of long-term toxicity and not a study of carcinogenicity. No information was provided on the identity or concentration of other chemicals contained in this formulation.] Survival was similar in treated and control rats. [No data on body weight were provided.] In female rats, there was an almost twofold increase in the incidence of tumours of the mammary gland (mainly fibroadenoma and adenocarcinoma) in animals exposed to the glyphosate-based formulation only versus control animals: control, 5/10 (50%); lowest dose, 9/10 (90%); intermediate dose, 10/10 (100%) [$P < 0.05$; Fisher exact test]; highest dose, 9/10 (90%). [The Working Group concluded that this study conducted on a glyphosate-based formulation was inadequate for evaluation because the number of animals per group was small, the histopathological description of tumours was poor, and incidences of tumours for individual animals were not provided.]

In another study with drinking-water, Chruscielska *et al.* (2000) gave groups of 55 male and 55 female Wistar rats (age, 6–7 weeks) drinking-water containing an ammonium salt of glyphosate as a 13.85% solution [purity of glyphosate, not reported] that was used to make aqueous solutions of 0 (control), 300, 900, and 2700 mg/L, for 24 months [details on the dosing regimen were not reported]. The authors reported that survival and body-weight gain were similar in treated and control animals. No significant increase in tumour incidence was reported in any of the treated groups. [The Working Group noted the limited information provided on dosing regimen, histopathological examination method, and tumour incidences.]

3.2.2 Dietary administration

The JMPR report included information on a 1-year feeding study in which groups of 24 male and 24 female Wistar-Alpk:APfSD rats [age at start not reported] were given diets containing glyphosate (purity, 95.6%) at a concentration of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 1 year (JMPR, 2006). There was a treatment-related decrease in body-weight gain at the two highest doses (significant at 20 000 ppm for both sexes, and at 8000 ppm only in females). There was no treatment-related decrease in survival. No significant increase in tumour incidence was observed in any of the treated groups. [The Working Group noted the short duration of exposure.]

The JMPR report also included information on a 104-week feeding study in which groups of 50 male and 50 female Sprague-Dawley rats [age at start not reported] were given diets containing glyphosate (purity, 98.7–98.9%) at a concentration that was adjusted to provide doses of 0, 10, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 weeks (JMPR, 2006). There was a treatment-related decrease in body-weight gain in males and females at the highest dose. There was no significant treatment-related decrease in survival or increase in tumour incidence in any of the treated groups.

Information was also included in the JMPR report on a 24-month feeding study in which groups of 52 male and 52 female Wistar-Alpk:APfSD rats [age at start not reported] were given diets containing glyphosate (purity, 97.6%) at a concentration of 0, 2000, 6000, or 20 000 ppm, ad libitum, for 24 months (JMPR, 2006). There was a treatment-related decrease in body-weight gain in males and females at the highest dose, and a corresponding significant increase in survival in males. No significant increase in tumour incidence was observed in any of the treated groups.

The EPA (1991a, b, c, d) provided information on a long-term study in which groups of 60 male and 60 female Sprague-Dawley rats (age, 8 weeks) were given diets containing glyphosate (technical grade; purity, 96.5%) at a concentration of 0 ppm, 2000 ppm, 8000 ppm, or 20 000 ppm, ad libitum, for 24 months. Ten animals per group were killed after 12 months. There was no compound-related effect on survival, and no statistically significant decreases in body-weight gain in male rats. In females at the highest dose, body-weight gain was significantly decreased, starting on day 51. In males at the lowest dose, there was a statistically significant increase in the incidence of pancreatic islet cell adenoma compared with controls: 8/57 (14%) versus 1/58 (2%), $P \leq 0.05$ (Fisher exact test). Additional analyses by the EPA (1991a) (using the Cochran–Armitage trend test and Fisher exact test, and excluding rats that died or were killed before week 55) revealed a statistically significant higher incidence of pancreatic islet cell adenoma in males at the lowest and highest doses compared with controls: lowest dose, 8/45 (18%; $P = 0.018$; pairwise test); intermediate dose, 5/49 (10%); highest dose, 7/48 (15%; $P = 0.042$; pairwise test) versus controls, 1/43 (2%). The range for historical controls for pancreatic islet cell adenoma reported in males at this laboratory was 1.8–8.5%. [The Working Group noted that there was no statistically significant positive trend in the incidence of these tumours, and no apparent progression to carcinoma.] There was also a statistically significant positive trend in the incidence of hepatocellular adenoma in

Table 3.2 Studies of carcinogenicity with glyphosate in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) 24 mo Séralini *et al.* (2014)	Drinking-water containing a glyphosate-based formulation at a concentration of 0 (control), 1.1 × 10^{-8}% (glyphosate, 5.0 × 10^{-5} mg/L), 0.09% (glyphosate, 400 mg/L) or 0.5% (glyphosate, 2.25 × 10^{3} mg/L), ad libitum, for 24 mo 10 M and 10 F/group (age, 5 wk)	*Males* No significant increase in tumour incidence observed in any of the treated groups *Females* Mammary tumours (mainly fibroadenomas and adenocarcinomas): 5/10 (50%), 9/10 (90%), 10/10 (100%)*, 9/10 (90%) Pituitary lesions (hypertrophy, hyperplasia, and adenoma): 6/10 (60%), 8/10 (80%), 7/10 (70%), 7/10 (70%)	 NS *[$P < 0.05$] [NS]	Data are from an in-depth life-long toxicology study on a glyphosate-based formulation and NK603 genetically modified maize; authors stated that the study was designed as a full chronic toxicity and not a carcinogenicity study. No information provided on the identity or concentration of other chemicals contained in this formulation Histopathology poorly described and tumour incidences for individual animals not discussed in detail. Small number of animals per group [The Working Group concluded this was an inadequate study for the evaluation of glyphosate carcinogenicity]
Rat, Wistar (M, F) 24 mo Chruscielska *et al.* (2000)	Drinking-water containing ammonium salt of glyphosate (13.85% solution) [purity of glyphosate, NR] was used to make aqueous solutions of 0, 300, 900, and 2700 mg/L [Details on dosing regimen, NR] 55 M and 55 F/group (age, 6–7 wk)	No significant increase in tumour incidence observed in any of the treated groups	NS	Limited information on dosing regimen, histopathological examination methods, and tumour incidences
Rat, Wistar-Alpk:APfSD (M, F) 1 yr JMPR (2006)	Diet containing glyphosate (purity, 95.6%) at concentrations of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 1 yr 24 M and 24 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	Short duration of exposure
Rat, Sprague-Dawley (M, F) 104 wk JMPR (2006)	Diet containing glyphosate (purity, 98.7–98.9%) at doses of 0, 10, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 wk 50 M and 50 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	
Rat, Wistar-Alpk:APfSD (M, F) 24 mo JMPR (2006)	Diet containing glyphosate (purity, 97.6%) at concentrations of 0, 2000, 6000, or 20 000 ppm, ad libitum, for 2 yr 52 M and 52 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat Sprague-Dawley (M, F) 24 mo EPA (1991a, b, c, d)	Diet containing glyphosate (technical grade; purity, 96.5%) at concentrations of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 24 mo 60 M and 60 F/group (age, 8 wk) 10 rats/group killed after 12 mo	*Males* *Pancreas (islet cell):* Adenoma: 1/58 (2%), 8/57 (14%)*, 5/60 (8%), 7/59 (12%) Carcinoma: 1/58 (2%), 0/57, 0/60, 0/59 Adenoma or carcinoma (combined): 2/58 (3%), 8/57 (14%), 5/60 (8%), 7/59 (12%) *Liver:* Hepatocellular adenoma: 2/60 (3%), 2/60 (3%), 3/60 (6%), 7/60 (12%) Hepatocellular carcinoma: 3/60 (5%), 2/60 (3%), 1/60 (2%), 2/60 (3%) *Females* *Pancreas (islet cell):* Adenoma: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 Carcinoma: 0/60, 0/60, 0/60, 0/59 Adenoma or carcinoma (combined): 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 *Thyroid:* C-cell adenoma: 2/60 (3%), 2/60 (3%), 6/60 (10%), 6/60 (10%) C-cell carcinoma: 0/60, 0/60, 1/60, 0/60	Adenoma, * $P \leq 0.05$ (Fisher exact test with Bonferroni inequality); see comments Adenoma, *P* for trend = 0.016; see comments NS Adenoma, *P* for trend = 0.031; see comments	Historical control range for pancreatic islet cell adenoma reported in males at this laboratory, 1.8–8.5% EPA (1991a) performed additional analyses using the Cochran–Armitage trend test and Fisher exact test, and excluding animals that died or were killed before wk 54–55: *Males* *Pancreas (islet cell):* Adenoma: 1/43 (2%), 8/45 (18%; *P* = 0.018), 5/49 (10%), 7/48 (15%; *P* = 0.042) Carcinoma: 1/43 (2%), 0/45 (0%), 0/49 (0%), 0/48 (0%) Adenoma or carcinoma (combined): 2/43 (5%), 8/45 (18%), 5/49 (10%), 7/48 (15%) [There was no statistically significant positive trend in the incidence of pancreatic tumours, and no apparent progression to carcinoma] *Liver:* Hepatocellular adenoma: 2/44 (5%; *P* for trend = 0.016), 2/45 (4%), 3/49 (6%), 7/48 (15%) Hepatocellular carcinoma: 3/44 (7%); 2/45 (4%), 1/49 (2%), 2/48 (4%) Hepatocellular adenoma or carcinoma (combined): 5/44 (11%), 4/45 (9%), 4/49 (8%), 9/48 (19%) [There was no apparent progression to carcinoma] *Females* *Thyroid:* C-cell adenoma: 2/57 (4%; *P* for trend = 0.031), 2/60 (3%), 6/59 (10%), 6/55 (11%) C-cell carcinoma: 0/57, 0/60, 1/59 (2%), 0/55 C-cell adenoma or carcinoma (combined): 2/57 (4%), 2/60 (3%), 7/59 (12%), 6/55 (11%) [There was no apparent progression to carcinoma]

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat Sprague-Dawley (M, F) Lifetime (up to 26 mo) EPA (1991a, b, c, d)	Diet containing glyphosate (purity, 98.7%) at concentrations of 0 ppm, 30 ppm (3 mg/kg bw per day), 100 ppm (10 mg/kg bw per day), 300 ppm (31 mg/kg bw per day), ad libitum, up to 26 mo 50 M and 50 F/group [age, NR]	*Males* *Pancreas (islet cell):* Adenoma: 0/50 (0%), 5/49* (10%), 2/50 (4%), 2/50 (4%) Carcinoma: 0/50 (0%), 0/49 (0%), 0/50 (0%), 1/50 (2%) Adenoma or carcinoma (combined): 0/50 (0%), 5/49 (10%), 2/50 (4%), 3/50 (6%) *Females* *Pancreas (islet cell):* Adenoma: 2/50 (4%), 1/50 (2%), 1/50 (2%), 0/50 (0%) Carcinoma: 0/50 (0%), 1/50 (2%), 1/50 (2%), 1/50 (2%) Adenoma or carcinoma (combined): 2/50 (10%), 2/50 (2%), 2/50 (74%), 1/50 (2%)	 Adenoma, *[*P* < 0.05; Fisher exact test] NS	 [There was no statistically significant positive trend in the incidence of pancreatic tumours, and no apparent progression to carcinoma]

bw, body weight; d, day; F, female; M, male; mo, month; NR, not reported; NS, not significant; wk, week; yr, year males (P = 0.016) and of thyroid follicular cell adenoma in females (P = 0.031). [The Working Group noted that there was no apparent progression to carcinoma for either tumour type.]

The EPA (1991a, b, c, d) provided information on another long-term study in which groups of 50 male and 50 female Sprague-Dawley rats [age at start not reported] were given diets containing glyphosate (purity, 98.7%) at a concentration of 0, 30 (3 mg/kg bw per day), 100 (10 mg/kg bw per day), or 300 ppm (31 mg/kg bw per day), ad libitum, for life (up to 26 months). No information was provided on body weight or survival of the study animals. An increase in the incidence of pancreatic islet cell adenoma was reported in males at the lowest dose: controls, 0/50 (0%); lowest dose, 5/49 (10%) [P < 0.05; Fisher exact test]; intermediate dose, 2/50 (4%); highest dose, 2/50 (4%). [The Working Group noted that there was no statistically significant positive dose-related trend in the incidence of these tumours, and no apparent progression to carcinoma.]

3.2.3 Review articles

Greim *et al.* (2015) have published a review article containing information on nine long-term bioassay feeding studies in rats. Of these studies, two had been submitted for review to the EPA (1991a, b, c, d), two to the JMPR (JMPR, 2006), and one had been published in the openly available scientific literature (Chruscielska *et al.*, 2000); these studies are discussed earlier in Section 3.2. The review article reported on an additional four long-term bioassay studies in rats that had not been previously published, but had been submitted to various organizations for registration purposes. The review article provided a brief summary of each study and referred to an online data supplement containing the original data on tumour incidence from study reports. The four additional long-term bioassay studies in rats are summarized below. [The Working Group did not evaluate these studies, which are not included in Table 3.2 and Section 5.3, because the information provided in the review article and its supplement was insufficient (e.g. information lacking on statistical methods, choice of doses, body-weight gain, survival data, details on histopathological examination and/or stability of dosed feed mixture).]

In one study (identified as Study 4, 1996), groups of 50 male and 50 female Wistar rats [age at start not reported] were given diets containing glyphosate (purity, 96%) at a concentration of 0, 100, 1000, or 10 000 ppm, ad libitum, for 24 months. It was reported that hepatocellular adenomas and hepatocellular carcinomas were found at non-statistically significant incidences in both males and females. There was no significant increase in tumour incidence in the treated groups. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In one study in Sprague-Dawley rats (identified as Study 5, 1997), groups of 50 male and 50 female rats [age at start not reported] were given diets containing glyphosate technical acid [purity not reported] at a concentration of 0, 3000, 15 000, or 25 000 ppm, ad libitum, for 24 months. There was no significant increase in tumour incidence in the treated groups. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In a second study in Sprague Dawley rats (identified as Study 6, 1997b), groups of 50 males and 50 females [age at start not reported] were given diets containing glyphosate (purity, 94.6–97.6%) at a concentration of 0, 3000, 10 000, or 30 000 ppm, ad libitum, for 24 months. Non-significant increases in tumour incidences compared with controls were noted for skin keratoacanthoma in males at the highest dose, and for fibroadenoma of the mammary gland in females at the lowest and intermediate doses. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In another study in male and female Wistar rats (identified as Study 8, 2009b), groups of 51 male and 51 female rats [age at start not reported] were fed diets containing glyphosate (purity, 95.7%) at a concentration of 0, 1500, 5000, or 15 000 ppm, ad libitum, for 24 months. The highest dose was progressively increased to reach 24 000 ppm by week 40. A non-significant increase in tumour incidence was noted for adenocarcinoma of the mammary gland in females at the highest dose (6/51) compared with controls (2/51). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information. The Working Group noted that tumours of the mammary gland had been observed in other studies in rats reviewed for the present *Monograph*.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Introduction

The herbicidal activity of glyphosate is attributed to interference with the production of essential aromatic amino acids (EPA, 1993b). In plants, glyphosate competitively inhibits the activity of enolpyruvylshikimate phosphate synthase, an enzyme that is not present in mammalian cells. Glyphosate is degraded by soil microbes to aminomethylphosphonic acid (AMPA) (see Fig. 4.1), a metabolite that can accumulate in the environment. In mammals, glyphosate is not metabolized efficiently, and is mainly excreted unchanged into the urine; however, it has been suggested that glyphosate can undergo gut microbial metabolism in humans (Motojyuku *et al.*, 2008) and rodents (Brewster *et al.*, 1991).

4.1.2 Absorption

(a) Humans

Data on the absorption of glyphosate via intake of food and water in humans were not available to the Working Group. Inhalation of glyphosate is considered to be a minor route of exposure in humans, because glyphosate is usually formulated as an isopropylamine salt with a very low vapour pressure (Tomlin, 2000).

In the Farm Family Exposure Study, 60% of farmers had detectable levels of glyphosate in 24-hour composite urine samples taken on the day they had applied a glyphosate-based formulation (Acquavella *et al.*, 2004). Farmers who did not use rubber gloves had higher urinary concentrations of glyphosate than those who did use gloves [indicating that dermal absorption is a relevant route of exposure]. In a separate study, detectable levels of glyphosate were found in urine samples from farm families and non-farm families (Curwin *et al.*, 2007).

In accidental and deliberate intoxication cases involving ingestion of glyphosate-based formulations, glyphosate was readily detectable in the blood (Zouaoui *et al.*, 2013). After deliberate or accidental ingestion, one glyphosate-based formulation was found to be more lethal to humans than another (Sørensen & Gregersen, 1999). [Greater lethality was attributed to the presence of trimethylsulfonium counterion, which might facilitate greater absorption after oral exposure.]

Small amounts of glyphosate can be absorbed after dermal exposures in humans in vitro. For example, when an aqueous solution of 1% glyphosate was applied in an in-vitro human skin model, only 1.4% of the applied dose was absorbed through the skin. Glyphosate is typically formulated as an isopropylamine salt, and is dissolved in a water-based vehicle, while the stratum corneum is a lipid-rich tissue (Wester et al., 1991). In-vitro studies using human skin showed that percutaneous absorption of a glyphosate-based formulation was no more than 2% of the administered dose over a concentration range of 0.5–154 μg/cm^2 and a topical volume range of 0.014–0.14 mL/cm^2. In addition, very little glyphosate (≤ 0.05% of the administered dose) was sequestered in the stratum corneum after dermal application (Wester et al., 1991).

In the human Caco-2 cell line, an in-vitro model of intestinal enterocytes, glyphosate (> 10 mg/mL) was shown to significantly disrupt barrier properties, leading to an increase in paracellular permeability (transport of substances that pass through the intercellular space between the cells) (Vasiluk et al., 2005).

(b) Experimental systems

Three studies have been conducted to investigate the absorption of a single oral dose of glyphosate in rats (Brewster et al., 1991; Chan & Mahler, 1992; EPA, 1993b).

In male Sprague-Dawley rats given [^{14}C]-labelled glyphosate (10 mg/kg bw), the majority of the radiolabel was associated with the gastrointestinal contents and small intestinal tissue 2 hours after administration (Brewster et al., 1991). Approximately 35–40% of the administered dose was found to be absorbed from the gastrointestinal tract. Urinary and faecal routes of elimination were equally important. [The Working Group concluded that glyphosate is incompletely absorbed from the gastrointestinal tract after oral exposure in rats.]

In a study by the United States National Toxicology Programme (NTP) in Fisher 344 rats, 30% of the administered oral dose (5.6 mg/kg bw) was absorbed, as determined by urinary excretion data (Chan & Mahler, 1992). This finding was in accordance with the previously described study of oral exposure in rats (Brewster et al., 1991).

In a study reviewed by the EPA, Sprague-Dawley rats were given an oral dose of glyphosate (10 mg/kg bw); 30% and 36% of the administered dose was absorbed in males and females, respectively (EPA, 1993b). At a dose that was ~10-fold higher (1000 mg/kg bw), oral absorption of glyphosate by the rats was slightly reduced.

In a 14-day feeding study in Wistar rats given glyphosate at dietary concentrations of up to 100 ppm, only ~15% of the administered dose was found to be absorbed (JMPR, 2006). In New Zealand White rabbits or lactating goats given glyphosate as single oral doses (6–9 mg/kg bw), a large percentage of the administered dose was recovered in the faeces [suggesting very poor gastrointestinal absorption of glyphosate in these animal models] (JMPR, 2006).

In monkeys given glyphosate by dermal application, percutaneous absorption was estimated to be between 1% and 2% of the administered dose (Wester et al., 1991). Most of the administered dose was removed by surface washes of the exposed skin.

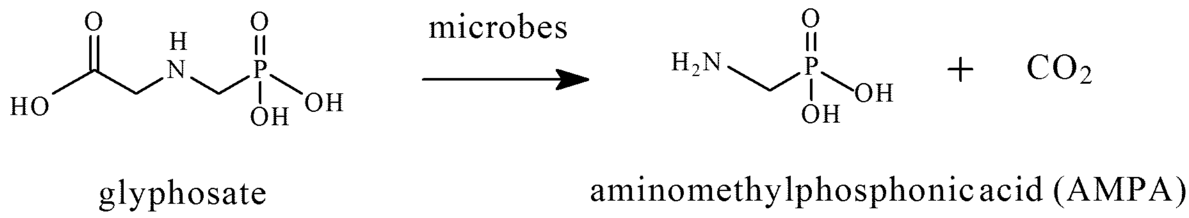
4.1.3 Distribution

(a) Humans

No data in humans on the distribution of glyphosate in systemic tissues other than blood were available to the Working Group. In cases of accidental or deliberate intoxication involving ingestion of glyphosate-based formulations, glyphosate was measured in blood. Mean blood concentrations of glyphosate were 61 mg/L and 4146 mg/L in mild-to-moderate cases of intoxication and in fatal cases, respectively (Zouaoui et al., 2013).

One report, using optical spectroscopy and molecular modelling, indicated that glyphosate could bind to human serum albumin, mainly by hydrogen bonding; however, the fraction of glyphosate that might bind to serum proteins in blood was not actually measured (Yue et al., 2008).

Fig. 4.1 Microbial metabolism of glyphosate to AMPA



Glyphosate is degraded to AMPA by microbial metabolism
Compiled by the Working Group

(b) Experimental systems

In Sprague-Dawley rats given a single oral dose of glyphosate (100 mg/kg bw), glyphosate concentrations in plasma reached peak levels, then declined slowly from day 1 to day 5 (Bernal *et al.*, 2010). The plasma data appeared to fit a one-compartment model with an elimination rate constant of k_{el} = 0.021 hour^{-1}. [The Working Group estimated the elimination half-life of glyphosate to be 33 hours.] Tissue levels of glyphosate were not determined in this study. In a study by Brewster *et al.* (1991), the tissue levels of glyphosate at 2, 6.3, 28, 96, and 168 hours in Sprague-Dawley rats given a single oral dose (10 mg/kg bw) declined rapidly. Tissues with the greatest amounts of detectable radiolabel (> 1% of the administered dose) were the small intestine, colon, kidney, and bone. Peak levels were reached in small intestine tissue and blood by 2 hours, while peak levels in other tissues occurred at 6.3 hours after dosing. After 7 days, the total body burden of [^{14}C]-labelled residues was ~1% of the administered dose, and was primarily associated with the bone (~1 ppm). In every tissue examined after administration of [^{14}C]-labelled glyphosate, essentially 100% of the radiolabel that was present in the tissue was unmetabolized parent glyphosate. Thus, essentially 100% of the body burden was parent compound, with no significant persistence of glyphosate after 7 days (Brewster *et al.*, 1991). In a 14-day feeding study in Wistar rats given diets containing glyphosate at 100 ppm, glyphosate reached steady-state levels in the blood by day 6 (JMPR, 2006). The tissue concentrations of glyphosate had the following rank order: kidneys > spleen > fat > liver. Tissue levels declined rapidly after cessation of exposure to glyphosate. A second study in rats given glyphosate (10 mg/kg bw per day, 14 days) followed by a single oral dose of [^{14}C]-glyphosate (at 10 mg/kg bw) showed that repeated dosing did not alter the tissue distribution of glyphosate (JMPR, 2006).

In rhesus monkeys, tissues harvested 7 days after dermal exposures to [^{14}C]-labelled glyphosate did not contain radiolabel at detectable levels (Wester *et al.*, 1991).

4.1.4 Metabolism and modulation of metabolic enzymes

(a) Metabolism

Glyphosate is degraded in the environment by soil microbes, primarily to AMPA and carbon dioxide (Fig. 4.1; Jacob *et al.*, 1988). A minor pathway for the degradation of glyphosate in bacteria (*Pseudomonas sp.* strain LBr) is via conversion to glycine (Jacob *et al.*, 1988). In a case of deliberate poisoning with a glyphosate-based formulation, small amounts of AMPA (15.1 µg/mL) were detectable in the blood (Motojyuku *et al.*, 2008) [suggesting that this pathway might also operate in humans]. In rats given a single high oral dose of glyphosate (100 mg/kg bw), small amounts of AMPA were detected in the plasma (Bernal *et al.*, 2010). In

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male Sprague-Dawley rats given an oral dose of glyphosate (10 mg/kg bw), a very small amount of AMPA (< 0.04% of the administered dose) was detected in the colon 2 hours after dosing; this was attributed to intestinal microbial metabolism (Brewster *et al.*, 1991).

(b) Modulation of metabolic enzymes

(i) Humans

In human hepatic cell lines, treatment with one of four glyphosate-based formulations produced by the same company was shown to enhance CYP3A4 and CYP1A2 levels, while glutathione transferase levels were reduced (Gasnier *et al.*, 2010). [The Working Group noted that it was not clear whether the effects were caused by glyphosate alone or by the adjuvants contained in the formulation.]

(ii) Experimental systems

Exposure of Wistar rats to a glyphosate-based formulation significantly altered some hepatic xenobiotic enzyme activities (Larsen *et al.*, 2014). Liver microsomes obtained from male and female rats treated with the formulation exhibited ~50% reductions in cytochrome P450 (CYP450) content compared with control (untreated) rats. However, opposing effects were observed when assessing 7-ethoxycoumarin *O*-deethylase activity (7-ECOD, a non-specific CYP450 substrate). Female rats treated with the glyphosate-based formulation exhibited a 57% increase in hepatic microsomal 7-ECOD activity compared with controls, while male rats treated with the formulation exhibited a 58% decrease in this activity (Larsen *et al.*, 2014). [The Working Group noted that it was not clear whether the effects were caused by glyphosate alone or by adjuvants contained in the formulation.]

4.1.5 Excretion

(a) Humans

Excretion of glyphosate in humans was documented in several biomonitoring studies. For example, as part of the Farm Family Exposure Study, urinary concentrations of glyphosate were evaluated immediately before, during, and after glyphosate application in 48 farmers and their spouses and children (Acquavella *et al.*, 2004). Dermal contact with glyphosate during mixing, loading, and application was considered to be the main route of exposure in the study. On the day the herbicide was applied, 60% of the farmers had detectable levels of glyphosate in 24-hour composite urine samples, as did 4% of their spouses and 12% of children. For farmers, the geometric mean concentration was 3 µg/L, the maximum value was 233 µg/L, and the highest estimated systemic dose was 0.004 mg/kg bw (Acquavella *et al.*, 2004). In a separate study, detectable levels of glyphosate were excreted in the urine of members of farm families and of non-farm families, with geometric means ranging from 1.2 to 2.7 µg/L (Curwin *et al.*, 2007).

In a study of a rural population living near areas sprayed for drug eradication in Colombia (see Section 1.4.1, Table 1.5), mean urinary glyphosate concentrations were 7.6 µg/L (range, undetectable to 130 µg/L) (Varona *et al.*, 2009). AMPA was detected in 4% of urine samples (arithmetic mean, 1.6 µg/L; range, undetectable to 56 µg/L).

(b) Experimental systems

In an NTP study in Fisher 344 rats given a single oral dose of [^{14}C]-labelled glyphosate (5.6 or 56 mg/kg bw), it was shown that > 90% of the radiolabel was eliminated in the urine and faeces within 72 hours (Chan & Mahler, 1992). In Sprague-Dawley rats given [^{14}C]-labelled glyphosate at an oral dose of 10 or 1000 mg/kg bw, ~60–70% of the administered dose was excreted in the faeces, and the remainder in the urine (EPA, 1993b). By either route, most (98%) of the administered dose was excreted as unchanged parent compound. AMPA was the only metabolite found in the urine (0.2–0.3% of the administered dose) and faeces (0.2–0.4% of the administered dose). [The large amount of glyphosate excreted in the faeces is consistent with its poor oral absorption.] Less than 0.3% of the administered dose was expired as carbon dioxide.

In rhesus monkeys given glyphosate as an intravenous dose (9 or 93 µg), > 95% of the administered dose was excreted in the urine (Wester *et al.*, 1991). Nearly all the administered dose was eliminated within 24 hours. In contrast, in rhesus monkeys given glyphosate by dermal application (5400 µg/20 cm^2), only 2.2% of the administered dose was excreted in the urine within 7 days (Wester *et al.*, 1991).

Overall, systemically absorbed glyphosate is not metabolized efficiently, and is mainly excreted unchanged into the urine.

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

Glyphosate has been studied for genotoxic potential in a wide variety of assays. Studies carried out in exposed humans, in human cells in vitro, in other mammals in vivo and in vitro, and in non-mammalian systems in vivo and in vitro, respectively, are summarized in Table 4.1, Table 4.2, Table 4.3, Table 4.4, and Table 4.5. [A review article by Kier & Kirkland (2013) summarized the results of published articles and unpublished reports of studies pertaining to the genotoxicity of glyphosate and glyphosate formulations. A supplement to this report contained information on 66 unpublished regulatory studies. The conclusions and data tables for each individual study were included in the supplement; however, the primary study reports from which these data were extracted were not available to the Working Group. The information provided in the supplement was insufficient regarding topics such as details of statistical methods, choice of the highest dose tested, and verification of the target tissue exposure. The Working Group determined that the information in the supplement to Kier & Kirkland (2013) did not meet the criteria for data inclusion as laid out in the Preamble to the *IARC Monographs*, being neither "reports that have been published or accepted for publication in the openly available scientific literature" nor "data from governmental reports that are publicly available" (IARC, 2006). The review article and supplement were not considered further in the evaluation.]

(a) Humans

(i) Studies in exposed humans

See Table 4.1

In exposed individuals (n = 24) living in northern Ecuador in areas sprayed with a glyphosate-based formulation, a statistically significant increase in DNA damage (DNA strand breaks) was observed in blood cells collected 2 weeks to 2 months after spraying (Paz-y-Miño *et al.*, 2007). The same authors studied blood cells from individuals (n = 92) in 10 communities in Ecuador's northern border, who were sampled 2 years after the last aerial spraying with a herbicide mix containing glyphosate, and showed that their karyotypes were normal compared with those of a control group (Paz-y-Miño *et al.*, 2011).

Bolognesi *et al.* (2009) studied community residents (137 women of reproductive age and their 137 spouses) from five regions in Colombia. In three regions with exposures to glyphosate-based formulations from aerial spraying, blood samples were taken from the same individuals at three time-points (before spraying (baseline), 5 days after spraying and 4 months after spraying) to determine the frequency of micronucleus formation in lymphocytes. The baseline frequency of binucleated cells with micronuclei was significantly higher in subjects from the three regions where there had been aerial spraying with glyphosate-formulations and in a fourth region with pesticide exposure (but not through aerial spraying), compared with a reference region (without use of pesticide). The frequency of micronucleus formation in peripheral blood lymphocytes was significantly increased, compared with baseline levels in the same individuals, after aerial spraying with glyphosate-based formulations in each of the three regions (see Table 4.1 ; Bolognesi *et al.*, 2009). Immediately after spraying, subjects who reported direct contact with the glyphosate-based spray showed a higher frequency of binucleated cells with micronuclei. However, the increase in frequency of micronucleus formation observed immediately after spraying was not consistent with the rates of application used in the regions, and there was no association between self-reported direct contact with pesticide sprays and frequency of binucleated cells with micronuclei. In subjects from one but not other regions, the frequency of binucleated cells with micronuclei was significantly decreased 4 months after spraying, compared with immediately after spraying.

(ii) Human cells in vitro

See Table 4.2

Glyphosate induced DNA strand breaks (as measured by the comet assay) in liver Hep-2 cells (Mañas *et al.*, 2009a), lymphocytes (Mladinic *et al.*, 2009b; Alvarez-Moya *et al.*, 2014), GM38 fibroblasts, the HT1080 fibrosarcoma cell line (Monroy *et al.*, 2005), and the TR146 buccal carcinoma line (Koller *et al.*, 2012). DNA strand breaks were induced by AMPA in Hep-2 cells (Mañas *et al.*, 2009b), and by a glyphosate-based formulation in the TR146 buccal carcinoma cell line (Koller *et al.*, 2012).

In human lymphocytes, AMPA (Mañas *et al.*, 2009b), but not glyphosate (Mañas *et al.*, 2009a), produced chromosomal aberrations. Glyphosate did not induce a concentration-related increase in micronucleus formation in human lymphocytes at levels estimated to correspond to occupational and residential exposure (Mladinic *et al.*, 2009a). Sister-chromatid exchange was induced by glyphosate (Bolognesi *et al.*, 1997), and by a glyphosate-based formulation (Vigfusson & Vyse, 1980; Bolognesi *et al.*, 1997) in human lymphocytes exposed in vitro.

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.3

The ability of glyphosate or a glyphosate-based formulation to induce DNA adducts was studied in mice given a single intraperitoneal dose. Glyphosate induced DNA adducts (8-hydroxy deoxyguanosine) in the liver, but not in the kidney, while a glyphosate-based formulation caused a slight increase in DNA adducts in the kidney, but not in the liver (Bolognesi *et al.*, 1997). Peluso *et al.* (1998) showed that a glyphosate-based formulation (glyphosate, 30.4%), but not glyphosate alone, caused DNA adducts (as detected by ^{32}P-DNA post-labelling) in mouse liver and kidney. Glyphosate and a glyphosate-based formulation produced DNA strand breaks in the liver and kidney after a single intraperitoneal dose (Bolognesi *et al.*, 1997).

In mice given a single dose of glyphosate by gavage, no genotoxic effect was observed by the dominant lethal test (EPA, 1980a).

After a single intraperitoneal dose, no chromosomal aberrations were observed in the bone marrow of rats treated with glyphosate (Li & Long 1988), while chromosomal aberrations were increased in the bone marrow of mice given a glyphosate-based formulation (glyphosate isopropylamine salt, ~41%) (Prasad *et al.*, 2009). A single oral dose of a glyphosate-based formulation did not cause chromosomal aberrations in mice (Dimitrov *et al.*, 2006).

In mice treated by intraperitoneal injection, a single dose of glyphosate did not cause

Table 4.1 Genetic and related effects of glyphosate in exposed humans

Tissue	Cell type (if specified)	End-point	Test	Description of exposure and controls	Response[a]/ significance	Comments	Reference
Blood	NR	DNA damage	DNA strand breaks, comet assay	24 exposed individuals in northern Ecuador; areas sprayed with glyphosate-based formulation (sampling 2 weeks to 2 months after spraying); control group was 21 non-exposed individuals	+ $P < 0.001$		Paz-y-Miño et al. (2007)
Blood	NR	Chromosomal damage	Chromosomal aberrations	92 individuals in 10 communities, northern border of Ecuador; sampling 2 years after last aerial spraying with herbicide mix containing glyphosate); control group was 90 healthy individuals from several provinces without background of smoking or exposure to genotoxic substances (hydrocarbons, X-rays, or pesticides)	–	182 karyotypes were considered normal [Smoking status, NR]	Paz-y-Miño et al. (2011)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	55 community residents, Nariño, Colombia; area with aerial glyphosate-based formulation spraying for coca and poppy eradication (glyphosate was tank-mixed with an adjuvant)	+ [$P < 0.001$]	P values for after spraying vs before spraying in the same individuals	Bolognesi et al. (2009)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	53 community residents, Putumayo, Colombia; area with aerial glyphosate-based formulation spraying for coca and poppy eradication (glyphosate was tank-mixed with an adjuvant)	+ [$P = 0.01$]	P values for after spraying vs before spraying in the same individuals	Bolognesi et al. (2009)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	27 community residents, Valle del Cauca, Colombia; area where glyphosate-based formulation was applied through aerial spraying for sugar-cane maturation (glyphosate was applied without adjuvant)	+ [$P < 0.001$]	P values for after spraying vs before spraying in the same individuals	Bolognesi et al. (2009)

[a] +, positive; –, negative
NR, not reported; vs, versus

micronucleus formation in the bone marrow (Rank *et al.*, 1993), although two daily doses did (Bolognesi *et al.*, 1997; Mañas *et al.*, 2009a). AMPA, the main metabolite of glyphosate, also produced micronucleus formation after two daily intraperitoneal doses (Mañas *et al.*, 2009b). Conflicting results for micronucleus induction were obtained in mice exposed intraperitoneally to a glyphosate-based formulation. A single dose of the formulation at up to 200 mg/kg bw did not induce micronucleus formation in the bone marrow in one study (Rank *et al.* 1993), while it did increase micronucleus formation at 25 mg/kg bw in another study (Prasad *et al.*, 2009). After two daily intraperitoneal doses, a glyphosate-based formulation did not induce micronucleus formation at up to 200 mg/kg bw according to Grisolia (2002), while Bolognesi *et al.* (1997) showed that the formulation did induce micronucleus formation at 450 mg/kg bw. In mice given a single oral dose of a glyphosate-based formulation at 1080 mg/kg bw, no induction of micronuclei was observed (Dimitrov *et al.*, 2006).

(ii) Non-human mammalian cells in vitro

See Table 4.4

Glyphosate did not induce unscheduled DNA synthesis in rat primary hepatocytes, or *Hprt* mutation (with or without metabolic activation) in Chinese hamster ovary cells (Li & Long, 1988).

In bovine lymphocytes, chromosomal aberrations were induced by glyphosate in one study (Lioi *et al.*, 1998), but not by a glyphosate formulation in another study (Siviková & Dianovský, 2006). Roustan *et al.* (2014) demonstrated, in the CHO-K1 ovary cell line, that glyphosate induced micronucleus formation only in the presence of metabolic activation, while AMPA induced micronucleus formation both with and without metabolic activation. Sister-chromatid exchange was observed in bovine lymphocytes exposed to glyphosate (Lioi *et al.*, 1998) or a glyphosate formulation (in the absence but not the presence of metabolic activation) (Siviková & Dianovský, 2006).

(iii) Non-mammalian systems in vivo

See Table 4.5

Fish and other species

In fish, glyphosate produced DNA strand breaks in the comet assay in sábalo (Moreno *et al.*, 2014), European eel (Guilherme *et al.*, 2012b), zebrafish (Lopes *et al.*, 2014), and Nile tilapia (Alvarez-Moya *et al.*, 2014). AMPA also induced DNA strand breaks in the comet assay in European eel (Guilherme *et al.*, 2014b). A glyphosate-based formulation produced DNA strand breaks in numerous fish species, such as European eel (Guilherme *et al.*, 2010, 2012b, 2014a; Marques *et al.*, 2014, 2015), sábalo (Cavalcante *et al.*, 2008; Moreno *et al.*, 2014), guppy (De Souza Filho *et al.*, 2013), bloch (Nwani *et al.*, 2013), neotropical fish *Corydoras paleatus* (de Castilhos Ghisi & Cestari, 2013), carp (Gholami-Seyedkolaei *et al.*, 2013), and goldfish (Cavaş & Könen, 2007).

AMPA, the main metabolite of glyphosate, induced erythrocytic nuclear abnormalities (kidney-shaped and lobed nuclei, binucleate or segmented nuclei and micronuclei) in European eel (Guilherme *et al.*, 2014b). Micronucleus formation was induced by different glyphosate-based formulations in various fish (Grisolia, 2002; Cavaş & Könen, 2007; De Souza Filho *et al.*, 2013; Vera-Candioti *et al.*, 2013).

Glyphosate-based formulations induced DNA strand breaks in other species, including caiman (Poletta *et al.*, 2009), frog (Meza-Joya *et al.*, 2013), tadpoles (Clements *et al.*, 1997), and snail (Mohamed, 2011), but not in oyster (Akcha *et al.*, 2012), clam (dos Santos & Martinez, 2014), and mussel glochidia (Conners & Black, 2004). In earthworms, one glyphosate-based formulation induced DNA strand breaks while two others did not (Piola *et al.*, 2013; Muangphra *et al.*, 2014), highlighting the potential importance of components other than the active ingredient in the formulation.

Table 4.2 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in human cells in vitro

Tissue, cell line	End-point	Test	Results[a]		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Glyphosate							
Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	3 mM [507.2 µg/mL]	$P < 0.01$; dose–response relationship ($r \geq 0.90$; $P < 0.05$)	Mañas et al. (2009a)
Lymphocytes	DNA damage	DNA strand breaks, standard and hOGG1 modified comet assay	+	+	3.5 µg/mL	With the hOGG1 modified comet assay, + S9, the increase was significant ($P < 0.01$) only at the highest dose tested (580 µg/mL)	Mladinic *et al.* (2009b)
Lymphocytes	DNA damage	DNA strand breaks, comet assay	+	NT	0.0007 mM [0.12 µg/mL]	$P \leq 0.01$	Alvarez-Moya *et al.* (2014)
Fibroblast GM 38	DNA damage	DNA strand breaks, comet assay	+	NT	4 mM [676 µg/mL]	$P < 0.001$	Monroy *et al.* (2005)
Fibroblast GM 5757	DNA damage	DNA strand breaks, comet assay	(+)	NT	75 mM [12 680 µg/mL]	Glyphosate (ineffective alone, data NR) increased strand breaks induced by H_2O_2 (40 or 50 µM) ($P < 0.004$ vs H_2O_2 alone)	Lueken *et al.* (2004)
Fibrosarcoma HT1080	DNA damage	DNA strand breaks, comet assay	+	NT	4.75 mM [803 µg/mL]	$P < 0.001$	Monroy *et al.* (2005)
Buccal carcinoma TR146	DNA damage	DNA strand breaks, SCGE assay	+	NT	20 µg/mL	Dose-dependent increase ($P \leq 0.05$)	Koller *et al.* (2012)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	NT	6 mM [1015 µg/mL]		Mañas *et al.* (2009a)
Lymphocytes	Chromosomal damage	Micronucleus formation	–	(+)	580 µg/mL	$P < 0.01$ at the highest exposure + S9 No concentration-related increase in micronuclei containing the centromere signal (C+)	Mladinic *et al.* (2009a)

Table 4.2 (continued)

Tissue, cell line	End-point	Test	Results[a]		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	1000 μg/mL	*P* < 0.05	Bolognesi *et al.* (1997)
AMPA							
Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	4.5 mM [500 μg/mL]	*P* < 0.05 at 4.5 mM; *P* < 0.01 at up to 7.5 mM Dose–response relationship (r ≥ 0.90; *P* < 0.05)	Mañas *et al.* (2009b)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	+	NT	1.8 mM [200 μg/mL]	*P* < 0.05	Mañas *et al.* (2009b)
Glyphosate-based formulations							
Liver HepG2	DNA damage	DNA strand breaks, comet assay	(+)	NT	5 ppm	Glyphosate, 400 g/L Dose-dependent increase; greatest increase at 10 ppm Statistical analysis, NR	Gasnier *et al.* (2009)
Buccal carcinoma TR146	DNA damage	DNA strand breaks, SCGE assay	+	NT	20 μg/mL	Glyphosate acid, 450g/L Dose-dependent increase (*P* ≤ 0.05)	Koller *et al.* (2012)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	250 μg/mL	*P* < 0.001 No growth at 25 mg/mL	Vigfusson & Vyse (1980)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	100 μg/mL	Glyphosate, 30.4% *P* < 0.05	Bolognesi *et al.* (1997)

[a] +, positive; -, negative; (+) or (-) positive/negative in a study with limited quality

AMPA, aminomethyl phosphonic acid; HID, highest ineffective dose; hOGG1, human 8-hydroxyguanosine DNA-glycosylase; LED, lowest effective dose; NR, not reported; NT, not tested; S9, 9000 × *g* supernatant; SCGE, single cell gel electrophoresis; vs, versus

Micronucleus formation was induced by a glyphosate-based formulation (glyphosate, 36%) in earthworms (Muangphra et al., 2014), and by a different glyphosate-based formulation in caiman (Poletta et al., 2009, 2011), and frog (Yadav et al., 2013).

Insects

In standard *Drosophila melanogaster*, glyphosate induced mutation in the test for somatic mutation and recombination, but not in a cross of flies characterized by an increased capacity for CYP450-dependent bioactivation (Kaya et al., 2000). A glyphosate-based formulation also caused sex-linked recessive lethal mutations in *Drosophila* (Kale et al., 1995).

Plants

In plants, glyphosate produced DNA damage in *Tradescantia* in the comet assay (Alvarez-Moya et al., 2011). Chromosomal aberration was induced after exposure to glyphosate in fenugreek (Siddiqui et al., 2012), and in onion in one study (Frescura et al., 2013), but not in another (Rank et al., 1993). A glyphosate-based formulation also induced chromosomal aberration in barley roots (Truta et al., 2011) and onion (Rank et al., 1993), but not in *Crepis capillaris* (hawksbeard) (Dimitrov et al., 2006). Micronucleus formation was not induced by glyphosate in *Vicia faba* bean (De Marco et al., 1992) or by a glyphosate-based formulation in *Crepis capillaris* (Dimitrov et al., 2006).

(iv) Non-mammalian systems in vitro

See Table 4.6

Glyphosate induced DNA strand breaks in erythrocytes of tilapia fish, as demonstrated by comet assay (Alvarez-Moya et al., 2014).

Glyphosate did not induce mutation in *Bacillus subtillis*, *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, or in *Escherichia coli* WP2, with or without metabolic activation (Li & Long, 1988). However, Rank et al. (1993) demonstrated that a glyphosate-based formulation was mutagenic in *S. typhimurium* TA98 in the absence of metabolic activation, and in *S. typhimurium* TA100 in the presence of metabolic activation.

4.2.2 Receptor-mediated mechanisms

(a) Sex-hormone pathway disruption

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

In hormone-dependent T47D breast cancer cells, the proliferative effects of glyphosate (10^{-6} to 1 µM) (see Section 4.2.4) and those of 17β-estradiol (the positive control) were mitigated by the estrogen receptor antagonist, ICI 182780; the proliferative effect of glyphosate was completely abrogated by the antagonist at a concentration of 10 nM (Thongprakaisang et al., 2013). Glyphosate also induced activation of the estrogen response element (ERE) in T47D breast cancer cells that were stably transfected with a triplet ERE-promoter-luciferase reporter gene construct. Incubation with ICI 182780 at 10 nM eliminated the response. When the transfected cells were incubated with both 17β-estradiol and glyphosate, the effect of 17β-estradiol was reduced and glyphosate behaved as an estrogen antagonist. After 6 hours of incubation, glyphosate increased levels of estrogen receptors ERα and ERβ in a dose-dependent manner in T47D cells; after 24 hours, only ERβ levels were increased and only at the highest dose of glyphosate. [These findings suggested that the proliferative effects of glyphosate on T47D cells are mediated by ER.]

In human hepatocarcinoma HepG2 cells, four glyphosate-based formulations produced by the same company had a marked effect on the activity and transcription of aromatase, while glyphosate alone differed from controls, but not significantly so (Gasnier et al., 2009).

Table 4.3 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-human mammals in vivo

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Glyphosate								
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA adducts, 8-OHdG by LC/UV	+	300 mg/kg bw	i.p.; 1×; sampled after 8 and 24 h	Single dose tested only $P < 0.05$ after 24 h	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA adducts, 8-OHdG by LC/UV	–	300 mg/kg bw	i.p.; 1×; sampled after 8 and 24 h	Single dose tested only	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M, F)	Kidney	DNA damage	DNA adducts, ^{32}P-DNA post labelling	–	270 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt	Peluso *et al.* (1998)
Mouse, Swiss CD1 (M, F)	Liver	DNA damage	DNA adducts, ^{32}P-DNA post labelling	–	270 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt	Peluso *et al.* (1998)
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA strand breaks, alkaline elution assay	+	300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Single dose tested only $P < 0.05$ after 4 h	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA strand breaks, alkaline elution assay	+	300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Single dose tested only $P < 0.05$ after 4 h	Bolognesi *et al.* (1997)
Mouse, CD-1 (M)	Uterus after mating	Mutation	Dominant lethal test	–	2000 mg/kg bw	Oral gavage; 1 ×	Proportion of early resorptions evaluated after mating of non-treated females with glyphosate-treated male mice	EPA (1980)
Rat, Sprague-Dawley (M, F)	Bone marrow	Chromosomal damage	Chromosomal aberrations	–	1000 mg/kg bw	i.p.; 1 ×; sampled after 6, 12 and 24 h	Single dose tested only	Li & Long (1988)
Mouse, NMRI-bom (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 1 ×; sampled after 24 and 48 h	Glyphosate isopropylamine salt	Rank *et al.* (1993)
Mouse, Swiss CD1 (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	300 mg/kg bw	i.p.; 2 × 150 mg/kg bw with 24 h interval; sampled 6 or 24 h after the last injection	Single dose tested only $P < 0.05$ after 24 h	Bolognesi *et al.* (1997)

Table 4.3 (continued)

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, Balb C (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	400 mg/kg bw	i.p.; one injection per 24 h, 2 × 200, sampled 24 h after the last injection	$P < 0.01$ at the highest dose (400 mg/kg bw)	Mañas et al. (2009a)
AMPA								
Mouse, Balb C (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	200 mg/kg bw	i.p.; one injection per 24 h, 2 × 100, sampled 24 h after the last injection	$P < 0.01$ at the lowest dose (200 mg/kg bw)	Mañas et al. (2009b)
Glyphosate-based formulations								
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA adducts, 8-OHdG by LC/UV	–	~300 mg/kg bw	i.p.; 1 ×, sampled after 8 and 24 h	Glyphosate, 30.4% Single dose tested only	Bolognesi et al. (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA adducts, 8-OHdG by LC/UV	+	~300 mg/kg bw	i.p.; 1 ×, sampled after 8 and 24 h	Glyphosate, 30.4% Single dose tested only $P < 0.05$	Bolognesi et al. (1997)
Mouse, Swiss CD1 (M, F)	Kidney	DNA damage	DNA adducts, ^{32}P-DNA post labelling	+	400 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 30.4%	Peluso et al. (1998)
Mouse, Swiss CD1 (M, F)	Liver	DNA damage	DNA adducts, ^{32}P-DNA post labelling	+	400 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 30.4%	Peluso et al. (1998)
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA strand breaks, alkaline elution assay	+	~300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Glyphosate, 30.4% Single dose tested only $P < 0.05$ only after 4 h	Bolognesi et al. (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA strand breaks, alkaline elution assay	+	~300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Glyphosate, 30.4% Single dose tested only $P < 0.05$ only after 4 h	Bolognesi et al. (1997)
Mouse, C57BL (M)	Bone marrow (PCE)	Chromosomal damage	Chromosomal aberrations	–	1080 mg/kg bw	p.o. in distilled water; 1 ×; sampled after 6, 24, 48, 72, 96 and 120 h	Single dose tested only	Dimitrov et al. (2006)

Table 4.3 (continued)

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, Swiss albino (M)	Bone marrow	Chromosomal damage	Chromosomal aberrations	+	25 mg/kg bw	i.p.; 1 ×; sampled after 24, 48 and 72 h	Glyphosate isopropylamine salt, > 41% The percentage of aberrant cells was increased vs control in a dose- and time-dependent manner ($P < 0.05$)	Prasad *et al.* (2009)
Mouse, NMRI-bom (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 480 g/L The percentage of PCE decreased	Rank *et al.* (1993)
Mouse, Swiss (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 2 × within 24 h interval and sampled 24 h after the last injection	Glyphosate isopropylammonium salt, 480 g/L	Grisolia (2002)
Mouse, Swiss albino (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	25 mg/kg bw	i.p.; 1 × ; sampled after 24, 48 and 72 h	Glyphosate isopropylamine salt, > 41% Significant induction of micronuclei vs control at both doses and all times ($P < 0.05$)	Prasad *et al.* (2009)
Mouse, Swiss CD1 (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	450 mg/kg bw	i.p.; 2 × 225 mg/kg with 24 h interval; sampled 6 or 24 h after the last injection	Glyphosate, 30.4% Single dose tested only $P < 0.05$ after 6 h and 24 h	Bolognesi *et al.* (1997)
Mouse, C57BL (M)	Bone marrow	Chromosomal damage	Micronucleus formation	–	1080 mg/kg bw	p.o. in distilled water; 1 × ; sampled after 24, 48, 72, 96 and 120 h	Single dose tested only	Dimitrov *et al.* (2006)

[a] +, positive; -, negative; (+) or (-) positive/negative in a study with limited quality
bw, body weight; F, female; h, hour; HID, highest effective dose; i.p., intraperitoneal; LC, liquid chromatography; LED, lowest effective dose; M, male; PCE, polychromatic erythrocytes; p.o., oral; 8-OHdG, 8-hydroxydeoxyguanosine; UV, ultraviolet

Table 4.4 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-human mammalian cells in vitro

Species	Tissue, cell line	End-point	Test	Results[a]		Dose (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Glyphosate								
Rat, Fisher F334	Hepatocytes	DNA damage	Unscheduled DNA synthesis	–	NT	125 µg/mL		Li & Long (1988)
Hamster, Chinese	CHO-K_1BH_4 ovary, cell line	Mutation	*Hprt* mutation	–	–	22 500 µg/mL		Li & Long (1988)
Bovine	Lymphocytes	Chromosomal damage	Chromosomal aberrations	+	NT	17 µM [3 µg/mL]	$P < 0.05$	Lioi *et al.* (1998)
Hamster, Chinese	CHO-K1 ovary cell line	Chromosomal damage	Micronucleus formation	–	+	10 µg/mL	$P \leq 0.001$, in the dark +S9 Negative –S9 in the dark or with light irradiation	Roustan *et al.* (2014)
Bovine	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	17 µM [3 µg/mL]	$P < 0.05$	Lioi *et al.* (1998)
AMPA								
Hamster, Chinese	CHO-K1 ovary cell line	Chromosomal damage	Micronucleus formation	+	+	0.01 µg/mL	$P \leq 0.05$, in the dark –S9 Highest increase was observed at very low dose (0.0005 µg/mL) –S9 but with light-irradiation ($P < 0.01$)	Roustan *et al.* (2014)
Glyphosate-based formulations								
Bovine	Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	NT	1120 µM [190 µg/mL]	Glyphosate, 62%	Šivikova & Dianovský (2006)
Bovine	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	–	56 µM [9.5 µg/mL]	Glyphosate, 62% Time of exposure, 24 h $P < 0.01$, –S9, at ≥ 56 µM	Šivikova & Dianovský (2006)

[a] +, positive; –, negative; (+), weakly positive

AMPA, aminomethyl phosphonic acid; HIC, highest ineffective concentration; *Hprt*, hypoxanthine guanine phosphoribosyl transferase gene; LEC, lowest effective concentration; NT, not tested

Table 4.5 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-mammalian systems in vivo

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Glyphosate							
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and gill cells	DNA damage	DNA strand breaks, comet assay	+	0.48 mg/L	Time of exposure 6, 24, and 96 h For erythrocytes, $P = 0.01$ after 6 h, and $P = 0.014$ after 96 h; no significant increase after 24 h For gill cells, $P = 0.02$ only after 6 h at 2.4 mg/L	Moreno *et al.* (2014)
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay	+	0.0179 mg/L	Time of exposure 1 and 3 days $P < 0.05$	Guilherme *et al.* (2012b)
Fish	*Danio rerio* (zebrafish) sperm	DNA damage	DNA strand breaks, acridine orange method	+	10 mg/L	After 96 h, DNA integrity was 78.3 ± 3.5%, significantly reduced from control (94.7 ± 0.9%) and 5 mg/L (92.6 ± 1.9%), ($P < 0.05$)	Lopes *et al.* (2014)
Fish	*Oreochromis niloticus* (Nile tilapia) branchial erythrocytes	DNA damage	DNA strand breaks, comet assay	+	7 μM [1.2 mg/L]	Time of exposure, 10 days $P < 0.001$ with concentrations ≥ 7 μM	Alvarez-Moya *et al.* (2014)
Oyster	Oyster spermatozoa	DNA damage	DNA strand breaks, comet assay	–	0.005 mg/L	Time of exposure, 1 h	Akcha *et al.* (2012)
Insect	*Drosophila* standard cross	Mutation	SMART	+	1 mM [0.169 mg/L]	Purity, 96% Increased frequency of small single spots (≥ 1 mM) and total spots (≥ 2 mM) $P = 0.05$	Kaya *et al.* (2000)
Insect	*Drosophila melanogaster*, high bioactivation cross	Mutation	SMART	–	10 mM [1.69 mg/L]	Purity, 96%	Kaya *et al.* (2000)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Plant systems	*Tradescantia* clone 4430 (spiderworts), staminal hair nuclei	DNA damage	DNA strand breaks, comet assay	+	0.0007 mM [0.12 μg/mL]	Glyphosate isopropylamine salt $P < 0.01$ for directly exposed nuclei (dose-dependent increase) and plants	Alvarez-Moya et al. (2011)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	+	3%	Single dose tested only Partial but significant reversal with distilled water	Frescura et al. (2013)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	–	2.88 μg/mL	Glyphosate isopropylamine	Rank et al. (1993)
Plant systems	*Trigonella foenum-graecum* L. (fenugreek)	Chromosomal damage	Chromosomal aberrations	+	0.2%	$P < 0.001$; positive dose–response relationship	Siddiqui et al. (2012)
Plant systems	*Vicia faba* (bean)	Chromosomal damage	Micronucleus formation	–	1400 ppm (1400 μg/g of soil)	Tested with two types of soil, but not without soil	De Marco et al. (1992)
AMPA							
Fish	*Anguilla anguilla* L. (European eel)	DNA damage	DNA strand breaks, comet assay	+	0.0118 mg/L	Time of exposure, 1 and 3 days $P < 0.05$ after 1 day of exposure	Guilherme et al. (2014b)
Fish	*Anguilla anguilla* L. (European eel)	Chromosomal damage	Other (ENA)	+	0.0236 mg/L	$P < 0.05$ only at highest dose after 3 day exposure (not after 1 day)	Guilherme et al. (2014b)
Glyphosate-based formulations							
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay	+	0.058 mg/L	$P < 0.05$ Positive dose–response relationship	Guilherme et al. (2010)
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.058 mg/L	Glyphosate-based formulation, 30.8% Time of exposure, 1 and 3 days With FPG, $P < 0.05$; with comet assay alone, $P < 0.05$ at 116 μg/L	Guilherme et al. (2012b)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.116 mg/L	Single dose tested only Time of exposure, 3 days; recovery from non-specific DNA damage, but not oxidative DNA damage, 14 days after exposure $P < 0.05$	Guilherme *et al.* (2014a)
Fish	*Anguilla anguilla* L. (European eel), liver	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.058 mg/L	Glyphosate-based formulation, 485 g/L Time of exposure, 3 days $P < 0.05$	Marques *et al.* (2014, 2015)
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and bronchial cells	DNA damage	DNA strand breaks, comet assay	+	10 mg/L	Single dose tested only, for 6, 24, and 96 h $P < 0.05$ for both erythrocytes and bronchial cells	Cavalcante *et al.* (2008)
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and gill cells	DNA damage	DNA strand breaks, comet assay	+	1 mg/L	Glyphosate-based formulation, 480 g/L Time of exposure, 6, 24 and 96 h $P < 0.001$ after 24 and 96 h in erythrocytes and 24 h in gill cells	Moreno *et al.* (2014)
Fish	*Poecilia reticulata* (guppy) gill erythrocytes	DNA damage	DNA strand breaks, comet assay	+	2.83 µL/L [1.833mg/L]	Glyphosate, 64.8%, m/v (648 g/L) $P < 0.05$	De Souza Filho *et al.* (2013)
Fish	*Channa punctatus* (bloch), blood and gill cells	DNA damage	DNA strand breaks, comet assay	+	3.25 mg/L	Exposure continued for 35 days; blood and gill cells collected on day 1, 7, 14, 21, 28 and 35 $P < 0.01$, for blood and gill cells; DNA damage increased with time and concentration	Nwani *et al.* (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Corydoras paleatus* (blue leopard corydoras, mottled corydoras and peppered catfish), blood and hepatic cells	DNA damage	DNA strand breaks, comet assay	+	0.0067 mg/L	Glyphosate, 48% (corresponding to 3.20 µg/L) Single dose tested only, for 3, 6, and 9 days $P < 0.01$, in blood and in liver cells	de Castilhos Ghisi & Cestari (2013)
Fish	*Cyprinus carpio* Linnaeus (carp), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	2 mg/L (10% LC_{50}, 96 h)	Glyphosate, equivalent to 360 g/L Single dose tested only, for 16 days $P < 0.01$	Gholami-Seyedkolaei *et al.* (2013)
Fish	*Carassius auratus* (goldfish), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	5 ppm	Glyphosate equivalent to 360 g/L Time of exposure, 2, 4 and 6 days After 48 h: $P < 0.05$ (5 mg/L) and $P < 0.001$ (10 and 15 mg/L)	Cavas & Könen (2007)
Fish	*Prochilodus lineatus* (sábalo) erythrocytes	Chromosomal damage	Micronucleus formation	–	10 mg/L	Single dose tested only, for 6, 24, and 96 h Nuclear abnormalities (lobed nuclei, segmented nuclei and kidney-shaped nuclei)	Cavalcante *et al.* (2008)
Fish	*Corydoras paleatus* (blue leopard corydoras, mottled corydoras and peppered catfish), blood and hepatic cells	Chromosomal damage	Micronucleus formation	–	0.0067 mg/L	Glyphosate, 48% (corresponding to 3.20 µg/L) Single dose tested only, for 3, 6 and 9 days	de Castilhos Ghisi & Cestari (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Tilapia rendalli* (redbreast tilapia) blood erythrocytes	Chromosomal damage	Micronucleus formation	+	42 mg/kg bw	Glyphosate, 480 g/L Increased frequency of micronucleus formation vs control ($P < 0.05$) in blood samples collected 4 days after a single intra-abdominal injection of 42, 85, or 170 mg/kg bw	Grisolia (2002)
Fish	*Carassius auratus* (goldfish), erythrocytes	Chromosomal damage	Micronucleus formation	+	5 ppm	Glyphosate equivalent to 360 g/L Time of exposure, 2, 4 and 6 days Statistically significant differences: 96 h ($P < 0.05$); 144 h ($P < 0.01$)	Cavas & Könen (2007)
Fish	*Poecilia reticulata* (guppy) gill erythrocytes	Chromosomal damage	Micronucleus formation, ENA	+	1.41 µL/L [0.914 mg/L]	Glyphosate, 64.8%, m/v (648 g/L) Micronucleus formation, $P < 0.01$ Other nuclear abnormalities, $P < 0.05$ at 1.41 to 5.65 µL/L; concentration-dependent ($r^2 = 0.99$)	De Souza Filho *et al.* (2013)
Fish	*Cnesterodon decemmaculatus* (Jenyns, 1842) peripheral blood erythrocytes	Chromosomal damage	Micronucleus formation	+	3.9 mg/L	Glyphosate, 48% Time of exposure, 48 and 96 h $P < 0.05$, with 3.9 and 7.8 mg/L for 48 and 96 h	Vera-Candioti *et al.* (2013)
Fish	*Cnesterodon decemmaculatus* (Jenyns, 1842) peripheral blood erythrocytes	Chromosomal damage	Micronucleus formation	+	22.9 mg/L	Glyphosate, 48% Time of exposure, 48 and 96 h $P < 0.01$, with 22.9 and 45.9 mg/L, and $P < 0.05$ at 68.8 mg/L, for 96 h	Vera-Candioti *et al.* (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Prochilodus lineatus* (sábalo) erythrocytes	Chromosomal damage	Chromosomal aberrations	–	10 mg/L	Single dose tested only, for 6, 24, and 96 h Nuclear abnormalities (lobed nuclei, segmented nuclei and kidney-shaped nuclei)	Cavalcante *et al.* (2008)
Fish	*Anguilla anguilla* L. (European eel), peripheral mature erythrocytes	Chromosomal damage	Other (ENA)	+	0.058 mg/L	Time of exposure, 1 and 3 days Chromosomal breakage and/or chromosomal segregational abnormalities after 3 days of exposure, $P < 0.05$	Guilherme *et al.* (2010)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	0.500 mg/egg	Glyphosate, 66.2% In-ovo exposure; blood sampling at the time of hatching $P < 0.05$ in both experiments (50–1000 µg/egg in experiment 1; 500–1750 µg/egg in experiment 2)	Poletta *et al.* (2009)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	DNA damage	DNA strand breaks, comet assay	–	19 800 mg/L	Glyphosate, 66.2% Single dose tested only; in-ovo exposure First spraying exposure at the beginning of incubation period, a second exposure on day 35, then incubation until hatching	Poletta *et al.* (2011)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	Chromosomal damage	Micronucleus fomation	+	0.500 mg/egg	Glyphosate, 66.2% In-ovo exposure; blood sampling at the time of hatching $P < 0.05$ in both experiments (50–1000 µg/egg in experiment 1; 500–1750 µg/egg in experiment 2)	Poletta *et al.* (2009)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	Chromosomal damage	Micronucleus fomation	+	19.8 g/L	Glyphosate, 66.2% One dose tested; in-ovo exposure First spraying exposure at the beginning of incubation period, a second exposure on day 35, then incubation until hatching. Micronucleus formation, $P < 0.001$ Damage index, $P < 0.001$	Poletta *et al.* (2011)
Frog tadpole	*Rana catesbeiana* (ouaouaron), blood	DNA damage	DNA strand breaks, comet assay	+	1.687 mg/L, p.o.	Time of exposure, 24 h $P < 0.05$, with 6.75 mg/L; and $P < 0.001$ with 27 mg/L (with 108 mg/L, all died within 24 h)	Clements *et al.* (1997)
Frog	*Eleutherodactylus johnstonei* (Antilles coqui), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	0.5 µg a.e./cm²	Glyphosate-based formulation, 480 g/L Exposure to an homogenate mist in a 300 cm² glass terrarium Time of exposure: 0.5, 1, 2, 4, 8 and 24 h $P < 0.05$	Meza-Joya *et al.* (2013)
Frog	*Euflictis cyanophlyctis* (Indian skittering frog), erythrocytes	Chromosomal damage	Micronucleus formation	+	1 mg a.e./L	Glyphosate isopropylamine salt, 41% Time of exposure: 24, 48, 72, and 96 h $P < 0.001$ at 24, 48, 72 and 96 h	Yadav *et al.* (2013)
Snail	*Biomphalaria alexandrina*, haemolymph	DNA damage	DNA strand breaks, comet assay	+	10 mg/L	Glyphosate, 48% Single dose tested only, for 24 h. The percentage of damaged DNA was 21% vs 4% (control) No statistical analysis	Mohamed (2011)
Oyster	Oysters, spermatozoa	DNA damage	DNA strand breaks, comet assay	–	5 µg/L	Glyphosate, 200 µg equivalent/L Time of exposure, 1 h	Akcha *et al.* (2012)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Clam	*Corbicula fluminea* (Asian clam) haemocytes	DNA damage	DNA strand breaks, comet assay	–	10 mg/L	Time of exposure, 96 h Significant increase when atrazine (2 or 10 mg/L) was added to glyphosate ($P < 0.05$) No increase after exposure to atrazine or glyphosate separately	dos Santos & Martinez (2014)
Mussels	*Utterbackia imbecillis* (Bivalvia: Unionidae) glochidia mussels (larvae)	DNA damage	DNA strand breaks, comet assay	–	5 mg/L	Glyphosate, 18% Doses tested: 2.5 and 5 mg/L for 24 h NOEC, 10.04 mg/L	Conners & Black (2004)
Worm	Earthworm, *Eisenia andrei*, coelomocytes	DNA damage	DNA strand breaks, comet assay	–	240 µg a.e./cm²	Monoammonium salt, 85.4%, a.e. Epidermic exposure during 72 h (on filter paper)	Piola *et al.* (2013)
Worm	Earthworm, *Eisenia andrei*, coelomocytes	DNA damage	DNA strand breaks, comet assay	+	15 µg a.e./cm²	Monoammonium salt, 72%, a.e. Epidermic exposure during 72 h (on filter paper) $P < 0.001$	Piola *et al.* (2013)
Worm	Earthworm, *Pheretima peguana*, coelomocytes	DNA damage	DNA strand breaks, comet assay	–	251.50 µg/cm²	Active ingredient, 36% (w/v) Epidermic exposure 48 h on filter paper; LC_{50}, 251.50 µg/cm²	Muangphra *et al.* (2014)
Worm	Earthworm, *Pheretima peguana*, coelomocytes	Chromosomal damage	Micronucleus formation	+	251.50 µg/cm²	Active ingredient, 36% (w/v) Exposure, 48 h on filter paper; LC_{50}, 251.50 µg/cm² filter paper $P < 0.05$, for total micro-, bi-, and trinuclei frequencies at 0.25 µg/cm²; when analysed separately, micro- and trinuclei frequencies significantly differed from controls only at the LC_{50}	Muangphra *et al.* (2014)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Insect	*Drosophila melanogaster*	Mutation	Sex-linked recessive lethal mutations	+	1 ppm	Single dose tested only $P < 0.001$	Kale *et al.* (1995)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	+	1.44 µg/mL	Glyphosate-based formulation, 480 g/L The doses of formulation were calculated as glyphosate isopropylamine $P < 0.005$	Rank *et al.* (1993)
Plant systems	*Crepis capillaris* (hawksbeard)	Chromosomal damage	Chromosomal aberrations	–	0.5%	The highest dose tested (1%) was toxic	Dimitrov *et al.* (2006)
Plant systems	*Hordeum vulgare* L. cv. Madalin (barley roots)	Chromosomal damage	Chromosomal aberrations	(+)	360 µg/mL (0.1%)	Reported as "significant"	Truta *et al.* (2011)
Plant systems	*Crepis capillaris* (hawksbeard)	Chromosomal damage	Micronucleus formation	–	0.5%	The highest dose tested (1%) was toxic	Dimitrov *et al.* (2006)

[a] +, positive; –, negative; (+) or (–) positive/negative in a study with limited quality

a.e., acid equivalent; AMPA, aminomethyl phosphonic acid; bw, body weight; ENA, erythrocytic nuclear abnormalities; Endo III, endonuclease III; FPG, formamidopyrimidine glycosylase; h, hour; HID, highest ineffective dose; LC_{50}, median lethal dose; LED, lowest effective dose; NOEC, no-observed effect concentration; p.o., oral; SMART, somatic mutation and recombination test

Table 4.6 Genetic and related effects of glyphosate and glyphosate-based formulations on non-mammalian systems in vitro

Phylogenetic class	Test system (species; strain)	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Glyphosate								
Eukaryote Fish	*Oreochromis niloticus* (Nile tilapia), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	NT	7 µM [1.2 µg/mL]	Glyphosate isopropylamine, 96% $P \leq 0.001$; positive dose–response relationship for doses ≥ 7 µM	Alvarez-Moya et al. (2014)
Prokaryote (bacteria)	*Scytonema javanicum* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone; single dose tested only) enhanced UVB-induced increases	Wang et al. (2012)
Prokaryote (bacteria)	*Anabaena spherica* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone; single dose tested only) enhanced UVB-induced increases	Chen et al. (2012)
Prokaryote (bacteria)	*Microcystis viridis* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone; single dose tested only) enhanced UVB-induced increases	Chen et al. (2012)
Prokaryote (bacteria)	*Bacillus B. subtilis*	Differential toxicity	Rec assay	–	NT	2000 µg/disk		Li & Long (1988)
Prokaryote (bacteria)	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 and TA100	Mutation	Reverse mutation	–	–	5000 µg/plate		Li & Long (1988)
Prokaryote (bacteria)	*Escherichia coli* WP2	Mutation	Reverse mutation	–	–	5000 µg/plate		Li & Long (1988)

Table 4.6 (continued)

Phylogenetic class	Test system (species; strain)	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Acellular systems	Prophage superhelical PM2 DNA	DNA damage	DNA strand breaks	(–)	NT	75 mM [12.7 mg/mL] (in combination with H_2O_2 (100 µM)	Glyphosate inhibited H_2O_2-induced damage of PM2 DNA at concentrations where synergism was observed in cellular DNA damage (data NR)	Lueken et al. (2004)
Glyphosate-based formulations								
Prokaryote (bacteria)	*Salmonella typhimurium* TA98	Mutation	Reverse mutation	+	–	360 µg/plate	Glyphosate isopropylammonium salt, 480 g/L	Rank et al. (1993)
Prokaryote (bacteria)	*Salmonella typhimirium* TA100	Mutation	Reverse mutation	–	+	720 µg/plate	Glyphosate isopropylammonium salt, 480 g/L	Rank et al. (1993)

[a] +, positive; –, negative; (+) or (–) positive/negative in a study with limited quality

FADU, fluorometric analysis of DNA unwinding; HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested; UVB, ultraviolet B

Additionally, although all four glyphosate-based formulations dramatically reduced the transcription of ERα and ERβ in ERE-transfected HepG2 cells, glyphosate alone had no significant effect. Glyphosate and all four formulations reduced androgen-receptor transcription in the breast cancer cell line MDA-MB453-kb2, which has a high level of androgen receptor, with the formulations showing greater activity than glyphosate alone.

In a human placental cell line derived from choriocarcinoma (JEG3 cells), 18 hours of exposure to a glyphosate-based formulation (IC_{50} = 0.04%) decreased aromatase activity (Richard *et al.*, 2005). Glyphosate alone was without effect. The concentrations used did not affect cell viability.

Glyphosate, at non-overtly toxic concentrations, decreased aromatase activity in fresh human placental microsomes and transformed human embryonic kidney cells (293) transfected with human aromatase cDNA (Benachour *et al.*, 2007). A glyphosate-based formulation, at non-overtly toxic concentrations, had the same effect. The formulation was more active at equivalent doses than glyphosate alone.

In human androgen receptor and ERα and ERβ reporter gene assays using the Chinese hamster ovary cell line (CHO-K1), glyphosate had neither agonist nor antagonist activity (Kojima *et al.*, 2004, 2010).

(ii) Non-human mammalian experimental systems

In vivo

No data were available to the Working Group.

In vitro

Benachour *et al.* (2007) and Richard *et al.* (2005) reported that glyphosate and a glyphosate-based formulation inhibited aromatase activity in microsomes derived from equine testis. Richard *et al.* (2005) reported an absorbance spectrum consistent with an interaction between a nitrogen atom of glyphosate and the active site of the purified equine aromatase enzyme.

In the mouse MA-10 Leydig cell tumour cell line, a glyphosate-based formulation (glyphosate, 180 mg/L) markedly reduced $[(Bu)_2]$ cAMP-stimulated progesterone production (Walsh *et al.*, 2000). The inhibition was dose-dependent, and occurred in the absence of toxicity or parallel reductions in total protein synthesis. In companion studies, the formulation also disrupted steroidogenic acute regulatory protein expression, which is critical for steroid hormone synthesis. Glyphosate alone did not affect steroidogenesis at any dose tested up to 100 µg/L. Forgacs *et al.* (2012) found that glyphosate (300 µM) had no effect on testosterone production in a novel murine Leydig cell line (BLTK1). Glyphosate did not modulate the effect of recombinant human chorionic gonadotropin, which served as the positive control for testosterone production.

(iii) Non-mammalian experimental systems

Gonadal tissue levels of testosterone, 17β-estradiol and total microsomal protein were significantly reduced in adult snails (*Biomphalaria alexandrina*) exposed for 3 weeks to a glyphosate-based formulation (glyphosate, 48%) at the LC_{10} (10% lethal concentration) (Omran & Salama, 2013). These effects persisted after a 2-week recovery period, although the impact on 17β-estradiol was reduced in the recovery animals. The formulation also induced marked degenerative changes in the ovotestis, including absence of almost all the gametogenesis stages. CYP450 1B1, measured by enzyme-linked immunosorbent assay (ELISA), was substantially increased in the treated snails, including after the recovery period.

Glyphosate (0.11 mg/L for 7 days) did not increase plasma vittelogenin levels in juvenile rainbow trout (Xie *et al.*, 2005).

(b) Other pathways

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Glyphosate did not exhibit agonist activity in an assay for a human pregnane X receptor (PXR) reporter gene in a CHO-K1 cell line (Kojima *et al.*, 2010).

(ii) Non-human mammalian experimental systems

In vivo

In rats, glyphosate (300 mg/kg bw, 5 days per week, for 2 weeks) had no effect on the formation of peroxisomes, or the activity of hepatic carnitine acetyltransferase and catalase, and did not cause hypolipidaemia, suggesting that glyphosate does not have peroxisome proliferator-activated receptor activity (Vainio *et al.*, 1983).

In vitro

Glyphosate was not an agonist for mouse peroxisome proliferator-activated receptors PPARα or PPARγ in reporter gene assays using CV-1 monkey kidney cells in vitro (Kojima *et al.*, 2010). Glyphosate was also not an agonist for the aryl hydrocarbon receptor in mouse hepatoma Hepa1c1c7 cells stably transfected with a reporter plasmid containing copies of dioxin-responsive element (Takeuchi *et al.*, 2008).

(iii) Non-mammalian experimental systems

As a follow-up to experiments in which injection of glyphosate, or incubation with a glyphosate-based formulation (glyphosate, 48%), caused chick and frog (*Xenopus laevis*) cephalic and neural crest terata characteristic of retinoic acid signalling dysfunction, Paganelli *et al.* (2010) measured retinoic acid activity in tadpoles exposed to a glyphosate-based formulation. Retinoic activity measured by a reporter gene assay was increased by the formulation, and a retinoic acid antagonist blocked the effect. This indicated a possible significant modulation of retinoic acid activity by glyphosate.

4.2.3 Oxidative stress, inflammation, and immunosuppression

(a) Oxidative stress

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Several studies examined the effects of glyphosate on oxidative stress parameters in the human keratinocyte cell line HaCaT. Gehin *et al.* (2005) found that a glyphosate-based formulation was cytotoxic to HaCaT cells, but that addition of antioxidants reduced cytotoxicity. Elie-Caille *et al.* (2010) showed that incubation of HaCaT cells with glyphosate at 21 mM (the half maximal inhibitory concentration for cytotoxicity, IC_{50}) for 18 hours increased production of hydrogen peroxide (H_2O_2) as shown by dichlorodihydrofluorescein diacetate assay. Similarly, George & Shukla (2013) exposed HaCaT cells to a glyphosate-based formulation (glyphosate, 41%; concentration, up to 0.1 mM) and evaluated oxidative stress using the dichlorodihydrofluorescein diacetate assay. The formulation (0.1 mM) increased maximum oxidant levels by approximately 90% compared with vehicle, an effect similar to that of H_2O_2 (100 mM). Pre-treatment of the cells with the antioxidant *N*-acetylcysteine abrogated generation of oxidants by both the formulation and by H_2O_2. *N*-Acetylcysteine also inhibited cell proliferation induced by the glyphosate-based formulation (0.1 mM). [The Working Group noted the recognized limitations of using dichlorodihydrofluorescein diacetate as a marker of oxidative stress (Bonini *et al.*, 2006; Kalyanaraman *et al.*, 2012), and that the studies that reported this end-point as the sole evidence for oxidative stress should thus be interpreted with caution.]

Chaufan *et al.* (2014) evaluated the effects of glyphosate, AMPA (the main metabolite of glyphosate), and a glyphosate-based formulation on oxidative stress in HepG2 cells. The formulation, but not glyphosate or AMPA, had adverse effects. Specifically, the formulation increased levels of reactive oxygen species, nitrotyrosine formation, superoxide dismutase activity, and glutathione, but did not have an effect on catalase or glutathione-*S*-transferase activities. Coalova *et al.* (2014) exposed Hep2 cells to a glyphosate-based formulation (glyphosate as isopropylamine salt, 48%) at the LC_{20} (concentration not otherwise specified) and evaluated various parameters of oxidative stress. Exposure to the formulation for 24 hours increased catalase activity and glutathione levels, but did not have an effect on superoxide dismutase or glutathione-*S*-transferase activity.

Using blood samples from non-smoking male donors, Mladinic *et al.* (2009b) examined the effects of in-vitro exposure to glyphosate on oxidative DNA damage in primary lymphocyte cultures and on lipid peroxidation in plasma. Both parameters were significantly elevated at glyphosate concentrations of 580 µg/mL (~3.4 mM), but not at lower concentrations. Kwiatkowska *et al.* (2014) examined the effects of glyphosate, its metabolite AMPA, and *N*-methylglyphosate (among other related compounds) in human erythrocytes isolated from healthy donors. The erythrocytes were exposed at concentrations of 0.01–5 mM for 1, 4, or 24 hours before flow cytometric measurement of the production of reactive oxygen species with dihydrorhodamine 123. Production of reactive oxygen species was increased by glyphosate (≥ 0.25 mM), AMPA (≥ 0.25 mM), and *N*-methylglyphosate (≥ 0.5 mM).

(ii) Non-human mammalian experimental systems

Most of the studies of oxidative stress and glyphosate were conducted in rats and mice, and examined a range of exposure durations, doses, preparations (glyphosate and glyphosate-based formulations), administration routes and tissues. In addition, various end-points were evaluated to determine whether oxidative stress is induced by exposure to glyphosate. Specifically, it was found that glyphosate induces production of free radicals and oxidative stress in mouse and rat tissues through alteration of antioxidant enzyme activity, depletion of glutathione, and increases in lipid peroxidation. Increases in biomarkers of oxidative stress upon exposure to glyphosate in vivo have been observed in blood plasma (Astiz *et al.*, 2009b), liver (Bolognesi *et al.*, 1997; Astiz *et al.*, 2009b), skin (George *et al.*, 2010), kidney (Bolognesi *et al.*, 1997; Astiz *et al.*, 2009b), and brain (Astiz *et al.*, 2009b). Several studies demonstrated similar effects with a glyphosate-based formulation in the liver (Bolognesi *et al.*, 1997; Cavuşoğlu *et al.*, 2011; Jasper *et al.*, 2012), kidney (Bolognesi *et al.*, 1997; Cavuşoğlu *et al.*, 2011) and brain (Cattani *et al.*, 2014), or with a pesticide mixture containing glyphosate in the testes (Astiz *et al.*, 2013). Pre-treatment with antioxidants has been shown to mitigate the induction of oxidative stress by a glyphosate-based formulation (Cavuşoğlu *et al.*, 2011) and by a pesticide mixture containing glyphosate (Astiz *et al.*, 2013).

DNA damage associated with oxidative stress after exposure to glyphosate (e.g. as reported in Bolognesi *et al.*, 1997) is reviewed in Section 4.2.1.

(iii) Non-mammalian experimental systems

Positive associations between exposure to glyphosate and oxidative stress were reported in various tissues in aquatic organisms (reviewed in Slaninova *et al.*, 2009). Glyphosate and various glyphosate-based formulations have been tested in various fish species for effects on a plethora of end-points (e.g. lipid peroxidation, DNA damage, expression of antioxidant enzymes, levels of glutathione), consistently presenting evidence that glyphosate can cause oxidative stress in fish (Lushchak *et al.*, 2009; Ferreira *et al.*, 2010; Guilherme *et al.*, 2010, 2012a, b, 2014a, b; Modesto & Martinez, 2010a, b; Cattaneo *et al.*, 2011; Glusczak *et al.*, 2011; de Menezes *et al.*, 2011; Ortiz-Ordoñez *et al.*, 2011; Nwani *et al.*, 2013; Marques *et al.*, 2014, 2015; Sinhorin *et al.*, 2014; Uren Webster *et al.*, 2014). Similar effects were observed in bullfrog tadpoles exposed to a glyphosate-based formulation (Costa *et al.*, 2008), and in the Pacific oyster exposed to a pesticide mixture containing glyphosate (Geret *et al.*, 2013).

(b) Inflammation and immunomodulation

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Nakashima *et al.* (2002) investigated the effects of glyphosate on cytokine production in human peripheral blood mononuclear cells. Glyphosate (1 mM) had a slight inhibitory effect on cell proliferation, and modestly inhibited the production of IFN-gamma and IL-2. The production of TNF-α and IL-1β was not affected by glyphosate at concentrations that significantly inhibited proliferative activity and T-cell-derived cytokine production.

(ii) Non-human mammalian experimental systems

Kumar *et al.* (2014) studied the pro-inflammatory effects of glyphosate and farm air samples in wildtype C57BL/6 and $TLR4^{-/-}$ mice, evaluating cellular response, humoral response, and lung function. In the bronchoalveolar lavage fluid and lung digests, airway exposure to glyphosate (1 or 100 µg) significantly increased the total cell count, eosinophils, neutrophils, and IgG1 and IgG2a levels. Airway exposure to glyphosate (100 ng, 1 µg, or 100 µg per day for 7 days) also produced substantial pulmonary inflammation, confirmed by histological examination. In addition, glyphosate-rich farm-air samples significantly increased circulating levels of IL-5, IL-10, IL-13 and IL-4 in wildtype and in $TLR4^{-/-}$ mice. Glyphosate was also tested in wildtype mice and significantly increased levels of IL-5, IL-10, IL-13, and IFN-γ (but not IL-4). The glyphosate-induced pro-inflammatory effects were similar to those induced by ovalbumin, and there were no additional or synergistic effects when ovalbumin was co-administered with glyphosate.

Pathological effects of glyphosate on the immune system have been reported in 13-week rat and mouse feeding studies by the NTP (Chan & Mahler, 1992). Relative thymus weight was decreased in male rats exposed for 13 weeks, but increased in male mice. Treatment-related changes in haematological parameters were observed in male rats at 13 weeks and included mild increases in haematocrit [erythrocyte volume fraction] and erythrocytes at 12 500, 25 000, and 50 000 ppm, haemoglobin at 25 000 and 50 000 ppm, and platelets at 50 000 ppm. In female rats, small but significant increases occurred in lymphocyte and platelet counts, leukocytes, mean corpuscular haemoglobin, and mean corpuscular volume at 13 weeks.

Blakley (1997) studied the humoral immune response in female CD-1 mice given drinking-water containing a glyphosate-based formulation at concentrations up to 1.05% for 26 days. The mice were inoculated with sheep erythrocytes to produce a T-lymphocyte, macrophage-dependent antibody response on day 21 of exposure. Antibody production was not affected by the formulation.

(iii) Non-mammalian experimental systems

A positive association between exposure to glyphosate and immunotoxicity in fish has been reported. Kreutz *et al.* (2011) reported alterations in haematological and immune-system parameters in silver catfish (*Rhamdia quelen*) exposed to sublethal concentrations (10% of the median lethal dose, LC_{50}, at 96 hours) of a glyphosate-based herbicide. Numbers of blood erythrocytes, thrombocytes, lymphocytes, and total leukocytes were significantly reduced after 96 hours of exposure, while the number of immature circulating cells was increased. The phagocytic index, serum bacteria agglutination, and total peroxidase activity were significantly reduced after 24 hours of exposure. Significant decreases in serum bacteria agglutination and lysozyme activity were found after 10 days of exposure. No effect on serum bactericidal and complement natural haemolytic activity was seen after 24 hours or 10 days of exposure to glyphosate.

el-Gendy *et al.* (1998) demonstrated effects of a glyphosate-based formulation (glyphosate, 48%) at 1/1000 of the concentration recommended for field application on humoral and cellular immune response in bolti fish (*Tilapia nilotica*). The mitogenic responses of splenocytes to phytohaemagglutinin, concanavalin A, and lipopolysaccharide in fish exposed to glyphosate for 96 hours were gradually decreased and reached maximum depression after 4 weeks. Glyphosate also produced a concentration-dependent suppression of in-vitro plaque-forming cells in response to sheep erythrocytes.

4.2.4 Cell proliferation and death

(a) Humans

(i) Studies in exposed humans

No data were available to the Working Group.

(ii) Human cells in vitro

Cell proliferation potential was explored in HaCaT keratinocytes exposed to a glyphosate-based formulation (glyphosate, 41%; concentration, up to 0.1 mM) (George & Shukla, 2013). The formulation increased the number of viable cells, as assessed by the MTT assay (based on reduction of the dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) at concentrations up to 0.1 mM, while concentration- and incubation-time-dependent reductions were seen at higher concentrations (up to 1 mM). The formulation (0.01 or 0.1 mM for 72 hours) significantly enhanced cell proliferation (measured by staining for either proliferating cell nuclear antigen or 5-bromo-2′-deoxyuridine); at 0.1 mM, the increases exceeded levels for the positive control, tetradecanoyl-phorbol-13-acetate. The proportion of S-phase cells (assessed using flow cytometry) and the expression of G1/S cell-cycle regulatory proteins (cyclins D1 and E, CDK2, CDK4, and CDK6) increased after exposure to the formulation or the positive control.

Li *et al.* (2013) reported that glyphosate and AMPA inhibited cell growth in eight human cancer cell lines, but not in two immortalized normal prostate cell lines. An ovarian (OVCAR-3) and a prostate (C4–2B) cell line showed the greatest loss in viability, with glyphosate or AMPA at 15–50 mM. Further assays were conducted on AMPA, but not glyphosate, in two prostate cancer cell lines (C4–2B and PC-3), and found cell-cycle arrest (decreased entry of cells into S-phase) and increased apoptosis. [The Working Group noted that the findings from these assays with AMPA are of unclear relevance to the effects of glyphosate.]

Glyphosate (10^{-6} to 1 μM) increased growth by 15–30% relative to controls in hormone-dependent T47D breast cancer cells, but only when endogenous estrogen was minimized in the culture medium (by substitution with 10% dextran-charcoal treated fetal bovine serum). Glyphosate did not affect the growth of hormone-independent MDA-MB231 breast cancer cells cultured in either medium (Thongprakaisang *et al.*, 2013).

Glyphosate (up to 30 μM) did not show cell proliferation potential (5-bromo-2′-deoxyuridine) and did not activate caspase 3 or TP53 in human neuroprogenitor ReN CX cells (Culbreth *et al.*, 2012).

Several studies evaluated the impact of glyphosate or glyphosate-based formulations on apoptotic cell death in the HepG2 human hepatoma cell line. Glyphosate-based formulations induced apoptosis in HepG2 cells, while glyphosate alone was generally without effect or showed effects at considerably higher concentrations (Gasnier *et al.*, 2009, 2010; Mesnage *et al.*, 2013; Chaufan *et al.*, 2014; Coalova *et al.*, 2014). For example, 23.5% of the nuclei of HepG2 cells exposed to a glyphosate-based formulation showed condensed and fragmented chromatin ($P < 0.01$), and caspases 3 and 7 were significantly activated, both effects being indicative of apoptosis (Chaufan *et al.*, 2014). Caspases were unaffected by glyphosate or AMPA alone. Glyphosate and AMPA did not affect cell viability at concentrations up to 1000 mg/L, a concentration that increased rather than decreased cell viability after 48 and 72 hours of incubation. In contrast, cells exposed to glyphosate-based formulation at lower concentrations were not viable. Similarly, Coalova *et al.* (2014) reported that a glyphosate-based formulation (glyphosate, 48%) induced apoptotic cell death in HepG2 cells. Apoptosis was indicated by activation of caspases 3 and 7, and the significant fraction (17.7%) of nuclei with condensed and fragmented chromatin ($P < 0.001$).

In studies with glyphosate and nine different glyphosate-based formulations in three cell lines, glyphosate alone did not increase the activity of adenylate kinase (Mesnage *et al.*, 2013). The activity of caspases 3 and 7 was significantly increased by glyphosate in HepG2 and embryonic kidney HEK293 cells, and elevated (although not significantly) about 1.8 times above control levels in placental choriocarcinoma JEG-3 cells. Two formulations containing an ethoxylated adjuvant induced adenylate kinase activity to a greater extent than caspase activity. All formulations were reported to be more cytotoxic than glyphosate. [In concentration–response curves, glyphosate showed an effect on mitochondrial succinate dehydrogenase activity, a measure of cell viability, that was similar to that shown by one formulation. The calculated 50% lethal concentration in JEG3 cells for mitochondrial succinate dehydrogenase activity was greater for three formulations, although the values appeared inconsistent with the concentration–response curves.]

In HUVEC primary neonate umbilical cord vein cells, and 293 embryonic kidney and JEG3 placental cell lines, Benachour & Séralini (2009) found that glyphosate at relatively high concentrations induced apoptosis, as indicated by induction of caspases 3 and 7, and DNA staining and microscopy. At comparable or lower concentrations, four glyphosate-based formulations all caused primarily necrotic cell death. The umbilical cord HUVEC cells were the most sensitive (by about 100-fold) to the apoptotic effects of glyphosate.

Heu *et al.* (2012) evaluated apoptosis in immortalized human keratinocytes (HaCaT) exposed to glyphosate (5–70 mM). Based on annexin V, propidium iodide and mitochondrial staining, exposures leading to 15% cytotoxicity gave evidence of early apoptosis, while increases in late apoptosis and necrosis were observed at higher levels of cytotoxicity.

(b) Non-human mammalian experimental systems

(i) In vivo

In male Wistar rats, glyphosate (10 mg/kg bw, injected intraperitoneally three times per week for 5 weeks) reduced, but not significantly, the inner mitochondrial membrane integrity of the substantia nigra and cerebral cortex (Astiz *et al.* 2009a). Caspase 3 activity was unaltered in these tissues. Mitochondrial cardiolipin content was significantly reduced, particularly in the substantia nigra, where calpain activity was substantially higher. Glyphosate induced DNA fragmentation in the brain and liver.

(ii) In vitro

In adult Sprague Dawley rat testicular cells exposed in vitro, glyphosate (up to 1%; for 24 or 48 hours) did not provoke cell-membrane alterations (Clair *et al.*, 2012). However, caspase 3 and 7 activity increased with exposure in Sertoli cells alone, and in Sertoli and germ cell mixtures. On the other hand, a glyphosate-based formulation (a 0.1% solution, containing 0.36 g/L of glyphosate) induced membrane alterations and decreased the activity of caspase 3 and 7 in Leydig cells, and in Sertoli and germ cell mixtures. In a separate study, glyphosate increased apoptosis in primary Sertoli cell cultures from mice (Zhao *et al.*, 2013).

Glyphosate (5–40 mM, for 12, 24, 48, or 72 hours) significantly increased cell death in a time- and concentration-dependent manner in differentiated rat pheochromocytoma PC12 (neuronal) cells Gui *et al.* (2012). Apoptotic changes included cell shrinkage, DNA fragmentation, decreased Bcl2 expression, and increased Bax expression. Both autophagy and apoptosis were implicated, as pre-treatment with the pan-caspase inhibitor Z-VAD or the autophagy inhibitor 3-MA inhibited cell loss.

Induction of apoptosis by glyphosate or glyphosate-based formulations was also studied in other cell lines. Glyphosate (10 µM) induced apoptosis in rat heart H9c2 cells, the effect being enhanced when glyphosate was given in combination with the adjuvant TN-20 (5 µM), (Kim *et al.*, 2013). A glyphosate-based formulation induced apoptosis in mouse 3T3-L1 fibroblasts, and inhibited their transformation to adipocytes (Martini *et al.*, 2012). A glyphosate-based formulation (10 mM) did not increase rat hepatoma HTC cell death, but did affect mitochondrial membrane potential (Malatesta *et al.*, 2008).

Glyphosate (up to 30 µM) did not activate caspase 3 or show cell proliferation potential (5-bromo-2′-deoxyuridine) in a mouse neuroprogenitor cell line, but did activate Tp53 at the highest concentration tested (Culbreth *et al.*, 2012).

4.2.5 Other mechanisms

No data on immortalization, epigenetic alterations, altered DNA repair, or genomic instability after exposure to glyphosate were available to the Working Group.

4.3 Data relevant to comparisons across agents and end-points

No data on high-throughput screening or other relevant data were available to the Working Group. Glyphosate was not tested by the Tox21 and ToxCast research programmes of the government of the USA (Kavlock *et al.* 2012; Tice *et al.*, 2013).

4.4 Cancer susceptibility data

No studies that examined genetic, life-stage, or other susceptibility factors with respect to adverse health outcomes that could be associated with exposure to glyphosate were identified by the Working Group.

4.5 Other adverse effects

4.5.1 Humans

In the USA in the past decade, poison-control centres have reported more than 4000 exposures to glyphosate-containing herbicides, of which several hundred were evaluated in a health-care facility, and fatalities were rare (Rumack, 2015). In a pesticide surveillance study carried out by the National Poisons Information Service of the United Kingdom, glyphosate was among the most common pesticide exposure implicated in severe or fatal poisoning cases between 2004 and 2013 (Perry *et al.*, 2014). Deliberate poisonings with glyphosate resulting in toxicity and fatality have been reported in many countries, including Australia (Stella & Ryan, 2004), Denmark (Mortensen *et al.*, 2000), India (Mahendrakar *et al.*, 2014), Japan (Motojyuku *et al.*, 2008), Republic of Korea (Park *et al.*, 2013), New Zealand (Temple & Smith, 1992), Sri Lanka (Roberts *et al.*, 2010), Taiwan, China (Chen *et al.*, 2009), and Thailand (Sribanditmongkol *et al.*, 2012).

Glyphosate demonstrated no potential for photo-irritation or photo-sensitization in 346 volunteers exposed dermally on normal or abraded skin (Hayes & Laws, 1991). On the other hand, Mariager *et al.* (2013) reported severe burns after prolonged accidental dermal exposure to a glyphosate-based formulation.

4.5.2 Experimental systems

Glyphosate was tested in nine regulatory submissions included in the Toxicity Reference Database (ToxRefDB) and reviewed by the EPA (EPA, 2015). Specifically, study design, treatment group, and treatment-related effect information were captured for four long-term studies and/or carcinogenicity studies, one short-term study, two multigeneration studies of reproductivity, and two studies of developmental toxicity. The NTP also tested glyphosate in a 13-week study in rats and mice (Chan & Mahler, 1992).

In a long-term combined study of toxicity and carcinogenicity in rats given glyphosate at nominal doses of 100, 400, and 1000 mg/kg bw per day, inflammation was observed in the stomach mucosa of females at the intermediate and highest doses (EPA, 1990, 1991b). In males at the highest dose, liver weight, cataracts and lens degeneration in the eyes, and urine specific gravity were increased, while body weight, body-weight gain, and urinary pH were decreased. Pancreatic acinar cell atrophy was observed in males at the highest dose. Pancreatic inflammation was also observed in male rats at the highest dose in a short-term study (nominal doses of 50, 250, and 1000 mg/kg bw per day) (EPA, 1987).

In the study by the NTP, cytoplasmic alteration was observed in the parotid and submandibular salivary glands of rats (Chan & Mahler, 1992).

In a study of carcinogenicity in mice given glyphosate at doses of 150, 1500, or 4500 mg/kg bw per day, liver hypertrophy and necrosis were observed in males at the highest dose (EPA, 1983). Other effects in males at the highest dose included increased testes weight, interstitial nephritis, and decreased body weight. In females at the highest dose, ovary weights were increased, proximal tubule epithelial basophilia and hypertrophy was observed, and body weights were decreased. In the study by the NTP, cytoplasmic alteration was observed in the parotid salivary glands in mice (Chan & Mahler, 1992).

Developmental and reproductive toxicity

In a study of developmental toxicity in rats given glyphosate at a dose of 300, 1000, or 3500 mg/kg bw per day, reduced implantation rates and fewer live fetuses were observed in dams at the highest dose (EPA, 1980b). In fetuses at the highest dose, unossified sternebra were observed and fetal weight was reduced.

5. Summary of Data Reported

5.1 Exposure data

Glyphosate is a broad-spectrum herbicide that is effective at killing or suppressing all plant types, including grasses, perennials, and woody plants. The herbicidal activity of glyphosate was discovered in 1970 and since then its use has increased to a point where it is now the most heavily used herbicide in the world, with an annual global production volume in 2012 of more than 700 000 tonnes used in more than 750 different products. Changes in farming practice and the development of genetically modified crops that are resistant to glyphosate have contributed to the increase in use.

There is little information available on occupational or community exposure to glyphosate. Glyphosate can be found in soil, air, surface water and groundwater, as well as in food. It has been detected in air during agricultural herbicide-spraying operations. Glyphosate was detected in urine in two studies of farmers in the USA, in urban populations in Europe, and in a rural population living near areas sprayed for drug eradication in Columbia. However, urinary concentrations were mostly below the limit of detection in several earlier studies of forestry workers who sprayed glyphosate. Exposure of the general population occurs mainly through diet.

5.2 Human carcinogenicity data

In its evaluation of the epidemiological studies reporting on cancer risks associated with exposure to glyphosate, the Working Group identified seven reports from the Agricultural Health Study (AHS) cohort and several reports from case–control studies. The AHS cohort, the pooled analyses of the case–control studies in the midwest USA, and the cross-Canada study were considered key investigations because of their relatively large size. Reports from two or more independent studies were available for non-Hodgkin lymphoma (NHL), multiple myeloma, Hodgkin lymphoma, glioma, and prostate. For the other cancer sites, results from only one study were available for evaluation.

5.2.1 NHL and other haematopoietic cancers

Two large case–control studies of NHL from Canada and the USA, and two case–control studies from Sweden reported statistically significant increased risks of NHL in association with exposure to glyphosate. For the study in Canada, the association was seen among those with more than 2 days/year of exposure, but no adjustment for other pesticides was done. The other three studies reported excesses for NHL associated with exposure to glyphosate, after adjustment for other pesticides (reported odds ratio were 2.1 (95% CI, 1.1–4.0); 1.85 (95% CI, 0.55–6.2); and 1.51 (95% CI, 0.77–2.94). Subtype-specific analyses in a Swedish case–control study indicated positive associations for total NHL, as well as all subtypes, but this association was statistically significant only for the subgroup of lymphocytic lymphoma/chronic lymphocytic leukaemia (OR, 3.35; 95% CI, 1.42–7.89). An elevated risk (OR, 3.1; 95% CI, 0.6–17.1) was also found for B-cell lymphoma in an European study based on few cases. One hospital-based case–control study from France did not find an association between exposure to glyphosate and NHL (OR, 1.0; 95% CI, 0.5–2.2) based on few exposed cases.

A roughly twofold excess of multiple myeloma, a subtype of NHL, was reported in three studies: only among the highest category of glyphosate use (> 2 days/year) in the large Canadian case–control study, in a case–control study from Iowa, USA, and in a French case–control study (all not statistically significant). These three studies did not adjust for the effect of other pesticides. In the AHS, there was no association with NHL (OR, 1.1; 0.7–1.9). For multiple myeloma, relative risk was 1.1 (95% CI, 0.5–2.4) when adjusted for age only; but was 2.6 (95% CI, 0.7–9.4) when adjusted for multiple confounders. No excess in leukaemia was observed in a case–control study in Iowa and Minnesota, USA, or in the AHS.

In summary, case–control studies in the USA, Canada, and Sweden reported increased risks for NHL associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. The AHS cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the risk estimates were statistically significant nor were they adjusted for other pesticide exposures.

5.2.2 Other cancer sites

No association of glyphosate with cancer of the brain in adults was found in the Upper Midwest Health case–control study. No associations in single case–control studies were found for cancers of the oesophagus and stomach, prostate, and soft-tissue sarcoma. For all other cancer sites (lung, oral cavity, colorectal, pancreas, kidney, bladder, breast, prostate, melanoma) investigated in the large AHS, no association with exposure to glyphosate was found.

5.3 Animal carcinogenicity data

Glyphosate was tested for carcinogenicity in male and female mice by dietary administration in two studies, and in male and female rats by dietary administration in five studies and in drinking-water in one study. A glyphosate-based formulation was also tested in drinking-water in one study in male and female rats, and by skin application in one initiation–promotion study in male mice.

There was a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. Renal tubule carcinoma is a rare tumour in this strain of mice. No significant increase in tumour incidence was seen in female mice in this study. In the second feeding study, there was a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice. No significant increase in tumour incidence was seen in female mice in this study.

For the five feeding studies in rats, two studies in the Sprague-Dawley strain showed a significant increase in the incidence of pancreatic islet cell adenoma in males – one of these two studies also showed a significant positive trend in the incidences of hepatocellular adenoma in males and of thyroid C-cell adenoma in females. Two studies (one in Sprague-Dawley rats, one in Wistar rats) found no significant increase in tumour incidence at any site. One study in Wistar rats was inadequate for the evaluation because of the short duration of exposure.

In the study in Wistar rats given drinking-water containing glyphosate, there was no significant increase in tumour incidence.

A glyphosate-based formulation was found to be a skin-tumour promoter in the initiation–promotion study in male Swiss mice. The study of a glyphosate-based formulation in drinking-water in Sprague-Dawley rats was inadequate for the evaluation because of the small number of animals per group, and the limited information provided on tumour histopathology and incidence in individual animals. These studies of a chemical mixture containing glyphosate were considered inadequate to evaluate the carcinogenicity of glyphosate alone.

5.4. Other relevant data

Direct data on absorption of glyphosate in humans were not available to the Working Group. Glyphosate was detected in the urine of agricultural workers in several studies, and in the blood of poisoning cases, indicative of absorption. Some evidence for absorption through human skin (~2%) was reported in studies in vitro. The minor role of dermal absorption was also shown in a study in non-human primate model in vivo. However, no study examined the rates of absorption in humans. In rodents, several studies showed up to 40% absorption after oral administration of a single or repeated dose.

Glyphosate was measured in human blood. No data on parenchymal tissue distribution for glyphosate in humans were available to the Working Group. In rats given glyphosate by oral administration, concentrations in tissues had the following rank order: kidneys > spleen > fat > liver. Repeated administration had no effect on the distribution of glyphosate. In a study in rats, the half-life of glyphosate in plasma was estimated to be more than 1 day, indicating that glyphosate is not rapidly eliminated.

In the environment, glyphosate is degraded by soil microbes, primarily to aminomethylphosphonic acid (AMPA) and carbon dioxide. Glyphosate is not efficiently metabolized in humans or other mammals. In rats, small amounts of AMPA were detected in the plasma and in the colon, with the latter being attributed to intestinal microbial metabolism. In humans, small amounts of AMPA are detectable in blood in cases of deliberate glyphosate poisoning. Few studies examined the possible effects of glyphosate-based formulations on metabolizing enzymes, but no firm conclusions could be drawn from these studies.

Studies in rodents showed that systemically absorbed glyphosate is excreted unchanged into the urine, and that the greatest amount is excreted in the faeces, indicating poor absorption. Glyphosate was detected in the urine of humans who were exposed occupationally to glyphosate. AMPA has also been detected in human urine.

Glyphosate is not electrophilic.

A large number of studies examined a wide range of end-points relevant to genotoxicity with glyphosate alone, glyphosate-based formulations, and AMPA.

There is strong evidence that glyphosate causes genotoxicity. The evidence base includes studies that gave largely positive results in human cells in vitro, in mammalian model systems in vivo and in vitro, and studies in other non-mammalian organisms. In-vivo studies in mammals gave generally positive results in the liver, with mixed results for the kidney and bone marrow. The end-points that have been evaluated in these studies comprise biomarkers of DNA adducts and various types of chromosomal damage. Tests in bacterial assays gave consistently negative results.

The evidence for genotoxicity caused by glyphosate-based formulations is strong. There were three studies of genotoxicity end-points in community residents exposed to glyphosate-based formulations, two of which reported positive associations. One of these studies examined chromosomal damage (micronucleus formation) in circulating blood cells before and after aerial spraying with glyphosate-based formulations and found a significant increase in micronucleus formation after exposure in three out of four different geographical areas. Additional evidence came from studies that gave largely positive results in human cells in vitro, in mammalian model systems in vivo and in vitro, and studies in other non-mammalian organisms. The end-points that were evaluated in these studies comprised biomarkers of DNA adducts and various types of chromosomal damage. The pattern of tissue specificity of genotoxicity end-points observed with glyphosate-based formulations is similar to that observed with glyphosate alone. Tests in bacterial assays gave generally negative results.

For AMPA, the evidence for genotoxicity is moderate. While the number of studies that examined the effects of AMPA was not large, all of the studies gave positive results. Specifically, genotoxicity was reported in a study in humans in vitro, a study in mammals in vivo, a study in mammals in vitro, and one study in eels in vivo.

Strong evidence exists that glyphosate, AMPA, and glyphosate-based formulations can induce oxidative stress. Evidence came from studies in many rodent tissues in vivo, and human cells in vitro. In some of these studies, the mechanism was challenged by co-administration of antioxidants and observed amelioration of the effects. Similar findings have been reported in fish and other aquatic species. Various end-points (e.g. lipid peroxidation markers, oxidative DNA adducts, dysregulation of antioxidant enzymes) have been evaluated in numerous studies. This increased the confidence of the Working Group in the overall database.

There is weak evidence that glyphosate or glyphosate-based formulations induce receptor-mediated effects. In multiple experiments, glyphosate-based formulations affected aromatase activity; glyphosate was active in a few of these studies. Some activity in other nuclear receptor-mediated pathways has been observed for glyphosate or glyphosate-based formulations. In one series of experiments, glyphosate was not found to be a ligand to several receptors and related proteins (aryl hydrocarbon receptor, peroxisome proliferator-activated receptors, pregnane X receptor).

There is weak evidence that glyphosate may affect cell proliferation or death. Several studies in human and rodent cell lines have reported cytotoxicity and cell death, the latter attributed to the apoptosis pathway. Studies that examined the effects of glyphosate alone or a glyphosate-based formulation found that glyphosate alone had no effect, or a weaker effect than the formulation.

There is weak evidence that glyphosate may affect the immune system, both the humoral and cellular response, upon long-term treatment in rodents. Several studies in fish, with glyphosate or its formulations, also reported immunosuppressive effects.

With regard to the other key characteristics of human carcinogens (IARC, 2014), the Working Group considered that the data were too few for an evaluation to be made.

Severe or fatal human poisoning cases have been documented worldwide. In rodents, organ and systemic toxicity from exposures to glyphosate are demonstrated by liver-weight effects and necrosis in animals at high doses. Additionally, effects on the pancreas, testes, kidney and ovaries, as well as reduced implantations and unossified sternebra were seen at similar doses.

No data on cancer-related susceptibility after exposure to glyphosate were available to the Working Group.

Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate.

6.3 Overall evaluation

Glyphosate is *probably carcinogenic to humans (Group 2A)*.

6.4 Rationale

In making this overall evaluation, the Working Group noted that the mechanistic and other relevant data support the classification of glyphosate in Group 2A.

In addition to limited evidence for the carcinogenicity of glyphosate in humans and sufficient evidence for the carcinogenicity of glyphosate in experimental animals, there is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens, and that these can be operative in humans. Specifically:

- There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals.

One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation) were significantly greater after exposure than before exposure in the same individuals.

- There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress.

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From: Akerman, Gregory
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate - CARC - Continues.....
Start Date/Time: Wed 9/16/2015 5:00:00 PM
End Date/Time: Wed 9/16/2015 8:00:00 PM

To: Ex. 6 - Personal Privacy
From: Akerman, Gregory
Sent: Wed 7/29/2015 5:48:03 PM
Subject: FW: Glyphosate - IARC Monograph
IARC Monograph.pdf

From: Rowland, Jess
Sent: Wednesday, July 29, 2015 1:47 PM
To: Akerman, Gregory; Dunbar, Anwar; Middleton, Karlyn; Wood, Charles; Lobdell, Danelle; Morton, Thurston
Cc: Housenger, Jack
Subject: Glyphosate - IARC Monograph

Hi Greg et al

Attached is the IARC Monograph. Perfect timing.

This will help us in the preparation of the CARC document.

Should be any trouble reading it……only 92 pages…!!

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

GLYPHOSATE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 1071-83-6 (acid); also relevant:
38641-94-0 (glyphosate-isopropylamine salt)
40465-66-5 (monoammonium salt)
69254-40-6 (diammonium salt)
34494-03-6 (glyphosate-sodium)
81591-81-3 (glyphosate-trimesium)

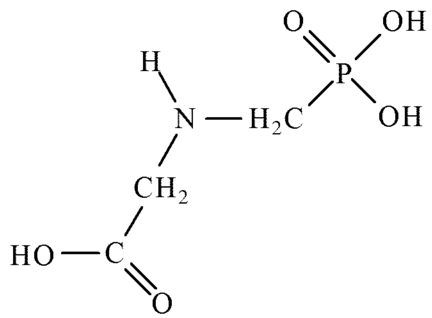
Chem. Abstr. Serv. Name: *N*-(phosphonomethyl)glycine

Preferred IUPAC Name: *N*-(phosphonomethyl)glycine

Synonyms: Gliphosate; glyphosate; glyphosate hydrochloride; glyphosate [calcium, copper (2+), dilithium, disodium, magnesium, monoammonium, monopotassium, monosodium, sodium, or zinc] salt

Trade names: Glyphosate products have been sold worldwide under numerous trade names, including: Abundit Extra; Credit; Xtreme; Glifonox; Glyphogan; Ground-Up; Rodeo; Roundup; Touchdown; Tragli; Wipe Out; Yerbimat (Farm Chemicals International, 2015).

1.1.2 Structural and molecular formulae and relative molecular mass



Molecular formula: $C_3H_8NO_5P$
Relative molecular mass: 169.07

Additional information on chemical structure is also available in the PubChem Compound database (NCBI, 2015).

1.1.3 Chemical and physical properties of the pure substance

Description: Glyphosate acid is a colourless, odourless, crystalline solid. It is formulated as a salt consisting of the deprotonated acid of glyphosate and a cation (isopropylamine, ammonium, or sodium), with more than one salt in some formulations.

Solubility: The acid is of medium solubility at 11.6 g/L in water (at 25 °C) and insoluble in common organic solvents such as acetone, ethanol, and xylene; the alkali-metal and amine salts are readily soluble in water (Tomlin, 2000).

Volatility: Vapour pressure, 1.31×10^{-2} mPa at 25 °C (negligible) (Tomlin, 2000).

Stability: Glyphosate is stable to hydrolysis in the range of pH 3 to pH 9, and relatively stable to photodegradation (Tomlin, 2000). Glyphosate is not readily hydrolysed or oxidized in the field (Rueppel *et al.*, 1977). It decomposes on heating, producing toxic fumes that include nitrogen oxides and phosphorus oxides (IPCS, 2005).

Reactivity: Attacks iron and galvanized steel (IPCS, 2005).

Octanol/water partition coefficient (P): log P, < −3.2 (pH 2–5, 20 °C) (OECD method 107) (Tomlin, 2000).

Henry's law: $< 2.1 \times 10^{-7}$ Pa m^3 mol^{-1} (Tomlin, 2000).

Conversion factor: Assuming normal temperature (25 °C) and pressure (101 kPa), mg/m^3 = 6.92 × ppm.

1.1.4 Technical products and impurities

Glyphosate is formulated as an isopropylamine, ammonium, or sodium salt in water-soluble concentrates and water-soluble granules. The relevant impurities in glyphosate technical concentrates are formaldehyde (maximum, 1.3 g/kg), *N*-nitrosoglyphosate (maximum, 1 mg/kg), and *N*-nitroso-*N*-phosphonomethyl glycine (FAO, 2000). Surfactants and sulfuric and phosphoric acids may be added to formulations of glyphosate, with type and concentration differing by formulation (IPCS, 1994).

1.2 Production and use

1.2.1 Production

(a) Manufacturing processes

Glyphosate was first synthesized in 1950 as a potential pharmaceutical compound, but its herbicidal activity was not discovered until it was re-synthesized and tested in 1970 (Székács & Darvas, 2012). The isopropylamine, sodium, and ammonium salts were introduced in 1974, and the trimesium (trimethylsulfonium) salt was introduced in Spain in 1989. The original patent protection expired outside the USA in 1991, and within the USA in 2000. Thereafter, production expanded to other major agrochemical manufacturers in the USA, Europe, Australia, and elsewhere (including large-scale production in China), but the leading preparation producer remained in the USA (Székács & Darvas, 2012).

There are two dominant families of commercial production of glyphosate, the "alkyl ester" pathways, predominant in China, and the "iminodiacetic acid" pathways, with iminodiacetic acid produced from iminodiacetonitrile (produced from hydrogen cyanide), diethanol amine, or chloroacetic acid (Dill *et al.*, 2010; Tian *et al.*, 2012).

To increase the solubility of technical-grade glyphosate acid in water, it is formulated as its isopropylamine, monoammonium, potassium, sodium, or trimesium salts. Most common is the isopropylamine salt, which is formulated as a liquid concentrate (active ingredient, 5.0–62%), ready-to-use liquid (active ingredient, 0.5–20%), pressurized liquid (active ingredient, 0.75–0.96%), solid (active ingredient, 76–94%), or pellet/tablet (active ingredient, 60–83%) (EPA, 1993a).

There are reportedly more than 750 products containing glyphosate for sale in the USA alone (NPIC, 2010). Formulated products contain various non-ionic surfactants, most notably polyethyloxylated tallowamine (POEA), to facilitate uptake by plants (Székács & Darvas, 2012). Formulations might contain other active ingredients, such as simasine, 2,4-dichlorophenoxyacetic acid (2,4-D), or 4-chloro-2-methylphenoxyacetic acid (IPCS, 1996), with herbicide resistance driving demand for new herbicide formulations containing multiple active ingredients (Freedonia, 2012).

(b) Production volume

Glyphosate is reported to be manufactured by at least 91 producers in 20 countries, including 53 in China, 9 in India, 5 in the USA, and others in Australia, Canada, Cyprus, Egypt, Germany, Guatemala, Hungary, Israel, Malaysia, Mexico, Singapore, Spain, Taiwan (China), Thailand, Turkey, the United Kingdom, and Venezuela (Farm Chemicals International, 2015). Glyphosate was registered in over 130 countries as of 2010 and is probably the most heavily used herbicide in the world, with an annual global production volume estimated at approximately 600 000 tonnes in 2008, rising to about 650 000 tonnes in 2011, and to 720 000 tonnes in 2012 (Dill *et al.*, 2010; CCM International, 2011; Hilton, 2012; Transparency Market Research, 2014).

Production and use of glyphosate have risen dramatically due to the expiry of patent protection (see above), with increased promotion of non-till agriculture, and with the introduction in 1996 of genetically modified glyphosate-tolerant crop varieties (Székács & Darvas, 2012). In the USA alone, more than 80 000 tonnes of glyphosate were used in 2007 (rising from less than 4000 tonnes in 1987) (EPA, 1997, 2011). This rapid growth rate was also observed in Asia, which accounted for 30% of world demand for glyphosate in 2012 (Transparency Market Research, 2014). In India, production increased from 308 tonnes in 2003–2004, to 2100 tonnes in 2007–2008 (Ministry of Chemicals & Fertilizers, 2008). China currently produces more than 40% of the global supply of glyphosate, exports almost 35% of the global supply (Hilton, 2012), and reportedly has sufficient production capacity to satisfy total global demand (Yin, 2011).

1.2.2 Uses

Glyphosate is a broad-spectrum, post-emergent, non-selective, systemic herbicide, which effectively kills or suppresses all plant types, including grasses, perennials, vines, shrubs, and trees. When applied at lower rates, glyphosate is a plant-growth regulator and desiccant. It has agricultural and non-agricultural uses throughout the world.

(a) Agriculture

Glyphosate is effective against more than 100 annual broadleaf weed and grass species, and more than 60 perennial weed species (Dill *et al.*, 2010). Application rates are about 1.5–2 kg/ha for pre-harvest, post-planting, and pre-emergence use; about 4.3 kg/ha as a directed spray in vines, orchards, pastures, forestry, and industrial weed control; and about 2 kg/ha as an aquatic herbicide (Tomlin, 2000). Common application methods include broadcast, aerial, spot, and directed spray applications (EPA, 1993a).

Due to its broad-spectrum activity, the use of glyphosate in agriculture was formerly limited to post-harvest treatments and weed control between established rows of tree, nut, and vine crops. Widespread adoption of no-till and conservation-till practices (which require chemical weed control while reducing soil erosion and labour and fuel costs) and the introduction of transgenic crop varieties engineered to be resistant to glyphosate have transformed glyphosate to a post-emergent, selective herbicide for use on annual crops (Duke & Powles, 2009; Dill *et al.* 2010). Glyphosate-resistant transgenic varieties have been widely adopted for the production of corn, cotton, canola, and soybean (Duke & Powles, 2009). Production of such crops accounted for 45% of worldwide demand for glyphosate in 2012 (Transparency Market Research, 2014). However, in Europe, where the planting of genetically modified crops has been largely restricted, post-harvest treatment is still the most common application of glyphosate (Glyphosate Task Force, 2014). Intense and continuous use of glyphosate has led to the emergence of resistant weeds that may reduce its effectiveness (Duke & Powles, 2009).

(b) Residential use

Glyphosate is widely used for household weed control throughout the world. In the USA, glyphosate was consistently ranked as the second most commonly used pesticide (after 2,4-D) in the home and garden market sector between 2001 and 2007, with an annual use of 2000–4000 tonnes (EPA, 2011).

(c) Other uses

Glyphosate was initially used to control perennial weeds on ditch banks and roadsides and under power lines (Dill *et al.*, 2010). It is also used to control invasive species in aquatic or wetland systems (Tu *et al.*, 2001). Approximately 1–2% of total glyphosate use in the USA is in forest management (Mance, 2012).

Glyphosate has been used in a large-scale aerial herbicide-spraying programme begun in 2000 to reduce the production of cocaine in Colombia (Lubick, 2009), and of marijuana in Mexico and South America (Székács & Darvas, 2012).

(d) Regulation

Glyphosate has been registered for use in at least 130 countries (Dill *et al.*, 2010). In the USA, all uses are eligible for registration on the basis of a finding that glyphosate “does not pose unreasonable risks or adverse effects to humans or the environment” (EPA, 1993a). A review conducted in 2001 in connection with the registration process in the European Union reached similar conclusions regarding animal and human safety, although the protection of groundwater during non-crop use was identified as requiring particular attention in the short term (European Commission, 2002).

Nevertheless, as worldwide rates of adoption of herbicide-resistant crops and of glyphosate use have risen in recent years (Duke & Powles, 2009), restriction of glyphosate use has been enacted or proposed in several countries, although documented actions are few. In 2013, the Legislative Assembly of El Salvador voted a ban on the use of pesticides containing glyphosate (República de El Salvador, 2013). Sri Lanka is reported to have instituted a partial ban based on an increasing number of cases of chronic kidney disease among agricultural workers, but the ban was lifted after 2 months (ColomboPage, 2014). The reasons for such actions have included the development of resistance among weed species, as well as health concerns.

No limits for occupational exposure were identified by the Working Group.

1.3 Measurement and analysis

Several methods exist for the measurement of glyphosate and its major metabolite aminomethyl phosphonic acid (AMPA) in various media, including air, water, urine, and serum (Table 1.1). The methods largely involve derivatization with 9-fluorenylmethyl chloro formate (FMOC-Cl) to reach sufficient retention in chromatographic columns (Kuang *et al.*, 2011; Botero-Coy *et al.*, 2013). Chromatographic techniques that do not require derivatization and enzyme-linked immunosorbent assays (ELISA) are under development (Sanchís *et al.*, 2012).

Table 1.1 Methods for the analysis of glyphosate

Sample matrix	Assay procedure	Limit of detection	Reference
Water	HPLC/MS (with online solid-phase extraction)	0.08 µg/L	Lee *et al.* (2001)
	ELISA	0.05 µg/L	Abraxis (2005)
	LC-LC-FD	0.02 µg/L	Hidalgo *et al.* (2004)
	Post HPLC column derivatization and FD	6.0 µg/L	EPA (1992)
	UV visible spectrophotometer (at 435 ng)	1.1 µg/L	Jan *et al.* (2009)
Soil	LC–MS/MS with triple quadrupole	0.02 mg/kg	Botero-Coy *et al.* (2013)
Dust	GC-MS-MID	0.0007 mg/kg	Curwin *et al.* (2005)
Air	HPLC/MS with online solid-phase extraction	0.01 ng/m³	Chang *et al.* (2011)
Fruits and vegetables	HILIC/WAX with ESI-MS/MS	1.2 µg/kg	Chen *et al.* (2013)
Field crops (rice, maize and soybean)	LC–ESI-MS/MS	0.007–0.12 mg/kg	Botero-Coy *et al.* (2013b)
Plant vegetation	HPLC with single polymeric amino column	0.3 mg/kg	Nedelkoska & Low (2004)
Serum	LC–MS/MS	0.03 µg/mL 0.02 µg/mL (aminomethylphosphonic acid) 0.01 µg/mL (3-methylphosphinicopropionic acid)	Yoshioka *et al.* (2011)
Urine	HPLC with post-column reaction and FD	1 µg/L	Acquavella *et al.* (2004)
	ELISA	0.9 µg/L	Curwin *et al.* (2007)

ELISA, enzyme-linked immunosorbent assay; ESI-MS/MS, electrospray tandem mass spectrometry; FD, fluorescence detection; GC-MS-MID, gas chromatography-mass spectrometry in multiple ion detection mode; HILIC/WAX, hydrophilic interaction/weak anion-exchange liquid chromatography; HPLC/MS, high-performance liquid chromatography with mass spectrometry; HPLC, high-performance liquid chromatography; LC-ESI–MS/MS, liquid chromatography-electrospray–tandem mass spectrometry; LC–LC, coupled-column liquid chromatography; LC–MS/MS, liquid chromatography–tandem mass spectrometry

1.4 Occurrence and exposure

1.4.1 Exposure

(a) Occupational exposure

Studies related to occupational exposure to glyphosate have included farmers and tree nursery workers in the USA, forestry workers in Canada and Finland, and municipal weed-control workers in the United Kingdom (Centre de Toxicologie du Québec, 1988; Jauhiainen *et al.*, 1991; Lavy *et al.*, 1992; Acquavella *et al.*, 2004; Johnson *et al.*, 2005). Para-occupational exposures to glyphosate have also been measured in farming families (Acquavella *et al.*, 2004; Curwin *et al.*, 2007). These studies are summarized in Table 1.2.

(b) Community exposure

Glyphosate can be found in soil, air, surface water, and groundwater (EPA, 1993a). Once in the environment, glyphosate is adsorbed to soil and is broken down by soil microbes to AMPA (Borggaard & Gimsing, 2008). In surface water, glyphosate is not readily broken down by water or sunlight (EPA, 1993a). Despite extensive worldwide use, there are relatively few studies

Table 1.2 Occupational and para-occupational exposure to glyphosate

Industry, country, year	Job/process	Results	Comments/additional data	Reference
Forestry				
Canada, 1986		Arithmetic mean of air glyphosate concentrations:	Air concentrations of glyphosate were measured at the work sites of one crew (five workers) during ground spraying 268 urine samples were collected from 40 workers; glyphosate concentration was above the LOD (15 µg/L) in 14%	Centre de Toxicologie du Québec (1988)
	Signaller	Morning, 0.63 µg/m ^{3} Afternoon, 2.25 µg/m ^{3}		
	Operator	Morning, 1.43 µg/m ^{3} Afternoon, 6.49 µg/m ^{3}		
	Overseer	Morning, 0.84 µg/m ^{3} Afternoon, 2.41 µg/m ^{3}		
	Mixer	Morning, 5.15 µg/m ^{3} Afternoon, 5.48 µg/m ^{3}		
Finland, year NR	Workers performing silvicultural clearing (*n* = 5)	Range of air glyphosate concentrations, < 1.25–15.7 µg/m ^{3} (mean, NR)	Clearing work was done with brush saws equipped with pressurized herbicide sprayers Air samples were taken from the workers' breathing zone (number of samples, NR) Urine samples were collected during the afternoons of the working week (number, NR) Glyphosate concentrations in urine were below the LOD (10 µg/L)	Jauhiainen *et al.* (1991)
USA, year NR	Workers in two tree nurseries (*n* = 14)	In dermal sampling, 1 of 78 dislodgeable residue samples were positive for glyphosate The body portions receiving the highest exposure were ankles and thighs	Dermal exposure was assessed with gauze patches attached to the clothing and hand rinsing Analysis of daily urine samples repeated over 12 weeks was negative for glyphosate	Lavy *et al.* (1992)
Weed control				
United Kingdom, year NR	Municipal weed control workers (*n* = 18)	Median, 16 mg/m ^{3} in 85% of 21 personal air samples for workers spraying with mechanized all-terrain vehicle Median, 0.12 mg/m ^{3} in 33% of 12 personal air samples collected from workers with backpack with lance applications	[The Working Group noted that the reported air concentrations were substantially higher than in other studies, but was unable to confirm whether the data were for glyphosate or total spray fluid] Dermal exposure was also measured, but reported as total spray fluid, rather than glyphosate	Johnson *et al.* (2005)

Table 1.2 (continued)

Industry, country, year	Job/process	Results	Comments/additional data	Reference
Farming				
USA, 2001	Occupational and para-occupational exposure of 24 farm families (24 fathers, 24 mothers and 65 children). Comparison group: 25 non-farm families (23 fathers, 24 mothers and 51 children)	Geometric mean (range) of glyphosate concentrations in urine: Non-farm fathers, 1.4 µg/L (0.13–5.4) Farm fathers, 1.9 µg/L (0.02–18) Non-farm mothers, 1.2 µg/L (0.06–5.0) Farm mothers, 1.5 µg/L (0.10–11) Non-farm children, 2.7 µg/L (0.10–9.4) Farm children, 2.0 µg/L (0.02–18)	Frequency of glyphosate detection ranged from 66% to 88% of samples (observed concentrations below the LOD were not censored). Detection frequency and geometric mean concentration were not significantly different between farm and non-farm families (observed concentrations below the LOD were not censored)	Curwin *et al.* (2007)
USA, year NR	Occupational and para-occupational exposures of 48 farmers, their spouses, and 79 children	Geometric mean (range) of glyphosate concentration in urine on day of application: Farmers, 3.2 µg/L (< 1 to 233 µg/L) Spouses, NR (< 1 to 3 µg/L) Children, NR (< 1 to 29 µg/L)	24-hour composite urine samples for each family member the day before, the day of, and for 3 days after a glyphosate application. Glyphosate was detected in 60% of farmers' samples, 4% of spouses' samples and 12% of children's samples the day of spraying and in 27% of farmers' samples, 2% of spouses' samples and 5% of children's samples 3 days after	Acquavella *et al.* (2004)

LOD, limit of detection; ND, not detected; NR, not reported on the environmental occurrence of glyphosate (Kolpin *et al.*, 2006).

(i) Air

Very few studies of glyphosate in air were available to the Working Group. Air and rain-water samples were collected during two growing seasons in agricultural areas in Indiana, Mississippi, and Iowa, USA (Chang *et al.*, 2011). The frequency of glyphosate detection ranged from 60% to 100% in air and rain samples, and concentrations ranged from < 0.01 to 9.1 ng/m^3 in air samples and from < 0.1 to 2.5 µg/L in rainwater samples. Atmospheric deposition was measured at three sites in Alberta, Canada. Rainfall and particulate matter were collected as total deposition at 7-day intervals throughout the growing season. Glyphosate deposition rates ranged from < 0.01 to 1.51 µg/m^2 per day (Humphries *et al.*, 2005).

No data were available to the Working Group regarding glyphosate concentrations in indoor air.

(ii) Water

Glyphosate in the soil can leach into ground-water, although the rate of leaching is believed to be low (Borggaard & Gimsing, 2008; Simonsen *et al.*, 2008). It can also reach surface waters by direct emission, atmospheric deposition, and by adsorption to soil particles suspended in runoff water (EPA, 1993a; Humphries *et al.*, 2005). Table 1.3 summarizes data on concentrations of glyphosate or AMPA in surface water and groundwater.

(iii) Residues in food and dietary intake

Glyphosate residues have been measured in cereals, fruits, and vegetables (Table 1.4). Residues were detected in 0.04% of 74 305 samples of fruits, vegetables, and cereals tested from 27 member states of the European Union, and from Norway, and Iceland in 2007 (EFSA, 2009). In cereals, residues were detected in 50% of samples tested in Denmark in 1998–1999, and in 9.5% of samples tested from member states of the European Union, and from Norway and Iceland in 2007 (Granby & Vahl, 2001; EFSA, 2009). In the United Kingdom, food sampling for glyphosate residues has concentrated mainly on cereals, including bread and flour. Glyphosate has been detected regularly and usually below the reporting limit (Pesticide Residues Committee, 2007, 2008, 2009, 2010). Six out of eight samples of tofu made from Brazilian soy contained glyphosate, with the highest level registered being 1.1 mg/kg (Pesticide Residues Committee, 2007).

(iv) Household exposure

In a survey of 246 California households, 14% were found to possess at least one product containing glyphosate (Guha *et al.*, 2013).

(v) Biological markers

Glyphosate concentrations in urine were analysed in urban populations in Europe, and in a rural population living near areas sprayed for drug eradication in Colombia (MLHB, 2013; Varona *et al.*, 2009). Glyphosate concentrations in Colombia were considerably higher than in Europe, with means of 7.6 ng/L and 0.02 µg/L, respectively (Table 1.5). In a study in Canada, glyphosate concentrations in serum ranged from undetectable to 93.6 ng/mL in non-pregnant women (n = 39), and were undetectable in serum of pregnant women (n = 30) and fetal cord serum (Aris & Leblanc, 2011).

1.4.2 Exposure assessment

Exposure assessment methods in epidemio-logical studies on glyphosate and cancer are discussed in Section 2.0 of the *Monograph* on Malathion, in the present volume.

Table 1.3 Concentration of glyphosate and AMPA in water

Country, year of sampling	Number of samples/setting	Results	Comments/additional data	Reference
USA, 2002	51 streams/agricultural areas (154 samples)	Maximum glyphosate concentration, 5.1 µg/L Maximum AMPA concentration, 3.67 µg/L	The samples were taken following pre- and post-emergence application and during harvest season Glyphosate detected in 36% of samples; AMPA detected in 69% of samples	Battaglin et al. (2005)
USA, 2002	10 wastewater treatment plants and two reference streams (40 samples)	Glyphosate, range ≤ 0.1–2 µg/L AMPA, range ≤ 0.1–4 µg/L	AMPA was detected more frequently (67.5%) than glyphosate (17.5%)	Kolpin et al. (2006)
Canada, 2002	3 wetlands and 10 agricultural streams (74 samples)	Range, < 0.02–6.08 µg/L	Glyphosate was detected in most of the wetlands and streams (22% of samples)	Humphries et al. (2005)
Colombia, year NR	5 areas near crops and coca eradication (24 samples)	Maximum concentration, 30.1 µg/L (minimum and mean, NR)	Glyphosate detected in 8% of samples (MDL, 25 µg/L)	Solomon et al. (2007)
Denmark, 2010–2012	4 agricultural sites (450 samples)	Range, < 0.1–31.0 µg/L	Glyphosate detected in 23% of samples; AMPA detected in 25% of samples	Brüch et al. (2013)

AMPA, aminomethylphosphonic acid; MDL, method detection limit; NR, data not reported

Table 1.4 Concentrations of glyphosate in food

Country, year	Type of food	Results	Comments/additional data	Reference
Denmark, 1998, 1999	Cereals	> 50% of samples had detectable residues Means: 0.08 mg/kg in 1999 and 0.11 mg/kg in 1998	49 samples of the 1998 harvest 46 samples of the 1999 harvest	Granby & Vahl (2001)
27 European Union member states, Norway and Iceland, 2007	350 different food commodities	0.04% of 2302 fruit, vegetable and cereal samples 9.5% of 409 cereal samples	74 305 total samples	EFSA (2009)
Australia, 2006	Composite sample of foods consumed in 24 hours	75% of samples had detectable residues Mean, 0.08 mg/kg Range, < 0.005 to 0.5 mg/kg	20 total samples from 43 pregnant women	McQueen *et al.* (2012)

Table 1.5 Concentrations of glyphosate and AMPA in urine and serum in the general population

Country, period	Subjects	Results	Comments/additional data	Reference
Urine				
18 European countries, 2013	162 individuals	Arithmetic mean of glyphosate concentration: 0.21 μg/L (maximum, 1.56 μg/L) Arithmetic mean of AMPA concentration: 0.19 μg/L (maximum, 2.63 μg/L)	44% of samples had quantifiable levels of glyphosate and 36% had quantifiable levels of AMPA	MLHB (2013)
Colombia, 2005–2006	112 residents of areas sprayed for drug eradication	Arithmetic mean (range) of glyphosate concentration: 7.6 μg/L (ND–130 μg/L) Arithmetic mean (range) of AMPA concentration: 1.6 μg/L (ND–56 μg/L)	40% of samples had detectable levels of glyphosate and 4% had detectable levels of AMPA (LODs, 0.5 and 1.0 μg/L, respectively) Urinary glyphosate was associated with use in agriculture	Varona *et al.* (2009)
Serum				
Canada, NR	30 pregnant women and 39 non-pregnant women	ND in serum of pregnant women or cord serum; Arithmetic mean, 73.6 μg/L, (range, ND–93.6 μg/L) in non-pregnant women	No subject had worked or lived with a spouse working in contact with pesticides LOD, 15 μg/L	Aris & Leblanc (2011)

AMPA, aminomethylphosphonic acid; LOD, limit of detection; ND, not detected; NR, not reported

2. Cancer in Humans

2.0 General discussion of epidemiological studies

A general discussion of the epidemiological studies on agents considered in Volume 112 of the *IARC Monographs* is presented in Section 2.0 of the *Monograph* on Malathion.

2.1 Cohort studies

See Table 2.1

The Agricultural Health Study (AHS), a large prospective cohort study conducted in Iowa and North Carolina in the USA, is the only cohort study to date to have published findings on exposure to glyphosate and the risk of cancer at many different sites (Alavanja *et al*., 1996; NIH, 2015) (see Section 2.0 of the *Monograph* on Malathion, in the present volume, for a detailed description of this study).

The enrolment questionnaire from the AHS sought information on the use of 50 pesticides (ever or never exposure), crops grown and livestock raised, personal protective equipment used, pesticide application methods used, other agricultural activities and exposures, nonfarm occupational exposures, and several lifestyle, medical, and dietary variables. The duration (years) and frequency (days per year) of use was investigated for 22 of the 50 pesticides in the enrolment questionnaire. [Blair *et al*. (2011) assessed the possible impact of misclassification of occupational pesticide exposure on relative risks, demonstrating that nondifferential exposure misclassification biases relative risk estimates towards the null in the AHS and tends to decrease the study power.]

The first report of cancer incidence associated with pesticide use in the AHS cohort considered cancer of the prostate (Alavanja *et al*., 2003). Risk estimates for exposure to glyphosate were not presented, but no significant exposure–response association with cancer of the prostate was found. In an updated analysis of the AHS (1993 to 2001), De Roos *et al*. (2005a) (see below) also found no association between exposure to glyphosate and cancer of the prostate (relative risk, RR, 1.1; 95% CI, 0.9–1.3) and no exposure–response trend (*P* value for trend = 0.69).

De Roos *et al*. (2005a) also evaluated associations between exposure to glyphosate and the incidence of cancer at several other sites. The prevalence of ever-use of glyphosate was 75.5% (> 97% of users were men). In this analysis, exposure to glyphosate was defined as: (a) ever personally mixed or applied products containing glyphosate; (b) cumulative lifetime days of use, or "cumulative exposure days" (years of use × days/year); and (c) intensity-weighted cumulative exposure days (years of use × days/year × estimated intensity level). Poisson regression was used to estimate exposure–response relations between exposure to glyphosate and incidence of all cancers combined, and incidence of 12 cancer types: lung, melanoma, multiple myeloma, and non-Hodgkin lymphoma (see Table 2.1) as well as oral cavity, colon, rectum, pancreas, kidney, bladder, prostate, and leukaemia (results not tabulated). Exposure to glyphosate was not associated with all cancers combined (RR, 1.0; 95% CI, 0.9–1.2; 2088 cases). For multiple myeloma, the relative risk was 1.1 (95% CI, 0.5–2.4; 32 cases) when adjusted for age, but was 2.6 (95% CI, 0.7–9.4) when adjusted for multiple confounders (age, smoking, other pesticides, alcohol consumption, family history of cancer, and education); in analyses by cumulative exposure-days and intensity-weighted exposure-days, the relative risks were around 2.0 in the highest tertiles. Furthermore, the association between multiple myeloma and exposure to glyphosate only appeared within the subgroup for which complete data were available on all the covariates; even without any adjustment, the risk of multiple myeloma associated with glyphosate use was increased by twofold among the smaller subgroup with available covariate data

Table 2.1 Cohort studies of cancer and exposure to glyphosate

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
De Roos et al. (2005a) Iowa and North Carolina, USA 1993–2001	54 315 (after exclusions, from a total cohort of 57 311) licensed pesticide applicators Exposure assessment method: questionnaire; semi-quantitative assessment from self-administered questionnaire	Lung	Ever use	147	0.9 (0.6–1.3)	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education	AHS Cancer sites investigated: lung, melanoma, multiple myeloma and NHL (results tabulated) as well as oral cavity, colon, rectum, pancreas, kidney, bladder, prostate and leukaemia (results not tabulated) [Strengths: large cohort; specific assessment of glyphosate; semiquantitative exposure assessment. Limitations: risk estimates based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]
			Cumulative exposure days:				
			1–20	40	1 (ref.)		
			21–56	26	0.9 (0.5–1.5)		
			57–2678	26	0.7 (0.4–1.2)		
			Trend-test *P* value: 0.21				
		Melanoma	Ever use	75	1.6 (0.8–3)		
			1–20	23	1 (ref.)		
			21–56	20	1.2 (0.7–2.3)		
			57–2678	14	0.9 (0.5–1.8)		
			Trend-test *P* value: 0.77				
		Multiple myeloma	Ever use	32	1.1 (0.5–2.4)	Age only (results in this row only)	
			Ever use	32	2.6 (0.7–9.4)		
			1–20	8	1 (ref.)		
			21–56	5	1.1 (0.4–3.5)		
			Trend-test *P* value: 0.27				
		NHL	Ever use	92	1.1 (0.7–1.9)		
			1–20	29	1 (ref.)		
			21–56	15	0.7 (0.4–1.4)		
			57–2678	17	0.9 (0.5–1.6)		
			Trend-test *P* value: 0.73				

Table 2.1 (continued)

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Flower *et al.* (2004) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up, 1975–1998	21 375; children (aged < 19 years) of licensed pesticide applicators in Iowa (n = 17 357) and North Carolina (n = 4018) Exposure assessment method: questionnaire	Childhood cancer	Maternal use of glyphosate (ever)	13	0.61 (0.32–1.16)	Child's age at enrolment	AHS Glyphosate results relate to the Iowa participants only [Strengths: Large cohort; specific assessment of glyphosate. Limitations: based on self-reported exposure; potential exposure to multiple pesticides; limited power for glyphosate exposure]
			Paternal use of glyphosate (prenatal)	6	0.84 (0.35–2.34)		
Engel *et al.* (2005) Iowa and North Carolina, USA Enrolment, 1993–1997 follow-up to 2000	30 454 wives of licensed pesticide applicators with no history of breast cancer at enrolment Exposure assessment method: questionnaire	Breast	Direct exposure to glyphosate	82	0.9 (0.7–1.1)	Age, race, state	AHS [Strengths: large cohort; specific assessment of glyphosate. Limitations: based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]
			Husband's use of glyphosate	109	1.3 (0.8–1.9)		
Lee *et al.* (2007) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up to 2002	56 813 licensed pesticide applicators Exposure assessment method: questionnaire	Colorectum	Exposed to glyphosate	225	1.2 (0.9–1.6)	Age, smoking, state, total days of any pesticide application	AHS [Strengths: large cohort. Limitations: based on self-reported exposure, limited to licensed applicators, potential
		Colon	Exposed to glyphosate	151			
		Rectum	Exposed to glyphosate	74			

Table 2.1 (continued)

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Andreotti *et al.* (2009) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up to 2004 Nested case–control study	Cases: 93 (response rate, NR); identified from population-based state-cancer registries. Incident cases diagnosed between enrolment and 31 December 2004 (> 9 years follow-up) included in the analysis. Participants with any type of prevalent cancer at enrolment were excluded. Vital status was obtained from the state death registries and the National Death Index. Participants who left North Carolina or Iowa were not subsequently followed for cancer occurrence. Controls: 82 503 (response rate, NR); cancer-free participants enrolled in the cohort Exposure assessment method: questionnaire providing detailed pesticide use, demographic and lifestyle information. Ever-use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) × (exposure intensity score)] of 13 pesticides was assessed	Pancreas (C25.0–C25.9)	Ever exposure to glyphosate	55	1.1 (0.6–1.7)	Age, smoking, diabetes	AHS [Strengths: large cohort. Limitations: based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]
			Low (< 185 days)	29			
			High (≥ 185 days)	19			
			Trend-test *P* value: 0.85				

AHS, Agricultural Health Study; NHL, non-Hodgkin lymphoma; NR, not reported

(De Roos *et al.*, 2005b). [The study had limited power for the analysis of multiple myeloma; there were missing data on covariates when multiple adjustments were done, limiting the interpretation of the findings.] A re-analysis of these data conducted by Sorahan (2015) confirmed that the excess risk of multiple myeloma was present only in the subset with no missing information (of 22 cases in the restricted data set). In a subsequent cross-sectional analysis of 678 male participants from the same cohort, Landgren *et al.* (2009) did not find an association between exposure to glyphosate and risk of monoclonal gammopathy of undetermined significance (MGUS), a premalignant plasma disorder that often precedes multiple myeloma (odds ratio, OR, 0.5; 95% CI, 0.2–1.0; 27 exposed cases).

Flower *et al.* (2004) reported the results of the analyses of risk of childhood cancer associated with pesticide application by parents in the AHS. The analyses for glyphosate were conducted among 17 357 children of Iowa pesticide applicators from the AHS. Parents provided data via questionnaires (1993–1997) and the cancer follow-up (retrospectively and prospectively) was done through the state cancer registries. Fifty incident childhood cancers were identified (1975–1998; age, 0–19 years). For all the children of the pesticide applicators, risk was increased for all childhood cancers combined, for all lymphomas combined, and for Hodgkin lymphoma, compared with the general population. The odds ratio for use of glyphosate and risk of childhood cancer was 0.61 (95% CI, 0.32–1.16; 13 exposed cases) for maternal use and 0.84 (95% CI, 0.35–2.34; 6 exposed cases) for paternal use. [The Working Group noted that this analysis had limited power to study a rare disease such as childhood cancer.]

Engel *et al.* (2005) reported on incidence of cancer of the breast among farmers' wives in the AHS cohort, which included 30 454 women with no history of cancer of the breast before enrolment in 1993–1997. Information on pesticide use and other factors was obtained at enrolment by self-administered questionnaire from the women and their husbands. A total of 309 incident cases of cancer of the breast were identified until 2000. There was no difference in incidence of cancer of the breast for women who reported ever applying pesticides compared with the general population. The relative risk for cancer of the breast among women who had personally used glyphosate was 0.9 (95% CI, 0.7–1.1; 82 cases) and 1.3 (95% CI, 0.8–1.9; 109 cases) among women who never used pesticides but whose husband had used glyphosate. [No information on duration of glyphosate use by the husband was presented.] Results for glyphosate were not further stratified by menopausal status.

Lee *et al.* (2007) investigated the relationship between exposure to agricultural pesticides and incidence of cancer of the colorectum in the AHS. A total of 56 813 pesticide applicators with no prior history of cancer of the colorectum were included in this analysis, and 305 incident cancers of the colorectum (colon, 212; rectum, 93) were diagnosed during the study period, 1993–2002. Most of the 50 pesticides studied were not associated with risk of cancer of the colorectum, and the relative risks with exposure to glyphosate were 1.2 (95% CI, 0.9–1.6), 1.0 (95% CI, 0.7–1.5), and 1.6 (95% CI, 0.9–2.9) for cancers of the colorectum, colon, and rectum, respectively.

Andreotti *et al.* (2009) examined associations between the use of pesticides and cancer of the pancreas using a case–control analysis nested in the AHS. This analysis included 93 incident cases of cancer of the pancreas (64 applicators, 29 spouses) and 82 503 cancer-free controls who completed the enrolment questionnaire. Ever-use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) × (exposure intensity score)] of 13 pesticides were assessed. Risk estimates were calculated controlling for age, smoking, and diabetes. The odds ratio for ever- versus never-exposure to glyphosate was

1.1 (95% CI, 0.6–1.7; 55 exposed cases), while the odds ratio for the highest category of level of intensity-weighted lifetime days was 1.2 (95% CI, 0.6–2.6; 19 exposed cases).

Dennis *et al.* (2010) reported that exposure to glyphosate was not associated with cutaneous melanoma within the AHS. [The authors did not report a risk estimate.]

2.2 Case–control studies on non-Hodgkin lymphoma, multiple myeloma, and leukaemia

2.2.1 Non-Hodgkin lymphoma

See Table 2.2

(a) *Case–control studies in the midwest USA*

Cantor *et al.* (1992) conducted a case–control study of incident non-Hodgkin lymphoma (NHL) among males in Iowa and Minnesota, USA (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). A total of 622 white men and 1245 population-based controls were interviewed in person. The association with farming occupation and specific agricultural exposures were evaluated. When compared with non-farmers, the odds ratios for NHL were 1.2 (95% CI, 1.0–1.5) for men who had ever farmed, and 1.1 (95% CI, 0.7–1.9; 26 exposed cases; adjusted for vital status, age, state, cigarette smoking status, family history of lymphohaematopoietic cancer, high-risk occupations, and high-risk exposures) for ever handling glyphosate. [There was low power to assess the risk of NHL associated with exposure to glyphosate. There was no adjustment for other pesticides. These data were included in the pooled analysis by De Roos *et al.* (2003).]

Brown *et al.* (1993) reported the results of a study to evaluate the association between multiple myeloma and agricultural risk factors in the midwest USA (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). A population-based case–control study of 173 white men with multiple myeloma and 650 controls was conducted in Iowa, USA, an area with a large farming population. A non-significantly elevated risk of multiple myeloma was seen among farmers compared with never-farmers. The odds ratio related to exposure to glyphosate was 1.7 (95% CI, 0.8–3.6; 11 exposed cases). [This study had limited power to assess the association between multiple myeloma and exposure to glyphosate. Multiple myeloma is now considered to be a subtype of NHL.]

De Roos *et al.* (2003) used pooled data from three case–control studies of NHL conducted in the 1980s in Nebraska (Zahm *et al.*, 1990), Kansas (Hoar *et al.*, 1986), and in Iowa and Minnesota (Cantor *et al.*, 1992) (see the *Monograph* on Malathion, Section 2.0, for a detailed description of these studies) to examine pesticide exposures in farming as risk factors for NHL in men. The study population included 870 cases and 2569 controls; 650 cases and 1933 controls were included for the analysis of 47 pesticides controlling for potential confounding by other pesticides. Both logistic regression and hierarchical regression (adjusted estimates were based on prior distributions for the pesticide effects, which provides more conservative estimates than logistic regression) were used in data analysis, and all models were essentially adjusted for age, study site, and other pesticides. Reported use of glyphosate as well as several individual pesticides was associated with increased incidence of NHL. Based on 36 cases exposed, the odds ratios for the association between exposure to glyphosate and NHL were 2.1 (95% CI, 1.1–4.0) in the logistic regression analyses and 1.6 (95% CI, 0.9–2.8) in the hierarchical regression analysis. [The numbers of cases and controls were lower than those in the pooled analysis by Waddell *et al.* (2001) because only subjects with no missing data on pesticides were included. The strengths of this study when compared with other studies are that it was large,

Table 2.2 Case–control studies of leukaemia and lymphoma and exposure to glyphosate

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
USA							
Brown *et al.* (1990) Iowa and Minnesota, USA 1981–1983	Cases: 578 (340 living, 238 deceased) (response rate, 86%); cancer registry or hospital records Controls: 1245 (820 living, 425 deceased) (response rate, 77–79%); random-digit dialling for those aged < 65 years and Medicare for those aged ≥ 65 years Exposure assessment method: questionnaire	Leukaemia	Any glyphosate	15	0.9 (0.5–1.6)	Age, vital status, state, tobacco use, family history lymphopoietic cancer, high-risk occupations, high risk exposures	[Strengths: large population based study in a farming area. Limitations: not controlled for exposure to other pesticides. Limited power for glyphosate exposure]
Cantor *et al.* (1992) Iowa and Minnesota, USA 1980–1982	Cases: 622 (response rate, 89.0%); Iowa health registry records and Minnesota hospital and pathology records Controls: 1245 (response rate, 76–79%); population-based; no cancer of the lympho-haematopoietic system; frequency-matched to cases by age (5-year group), vital status, state. Random-digit dialling (aged < 65 years); Medicare records (aged ≥ 65 years); state death certificate files (deceased subjects) Exposure assessment method: questionnaire; in-person interview	NHL	Ever handled glyphosate	26	1.1 (0.7–1.9)	Age, vital status, state, smoking status, family history lymphopoietic cancer, high-risk occupations, high-risk exposures	Data subsequentially pooled in De Roos *et al.* (2003); white men only [Strengths: large population-based study in farming areas. Limitations: not controlled for exposure to other pesticides. Limited power for glyphosate exposure]

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Brown et al. (1993) Iowa, USA 1981–1984	Cases: 173 (response rate, 84%); Iowa health registry Controls: 650 (response rate, 78%); Random-digit dialling (aged < 65 years) and Medicare (aged > 65 years) Exposure assessment method: questionnaire	Multiple myeloma	Any glyphosate	11	1.7 (0.8–3.6)	Age, vital status	[Strengths: population-based study. Areas with high prevalence of farming. Limitations: limited power for glyphosate exposure]
De Roos et al. (2003) Nebraska, Iowa, Minnesota, Kansas, USA 1979–1986	Cases: 650 (response rate, 74.7%); cancer registries and hospital records Controls: 1933 (response rate, 75.2%); random-digit dialling, Medicare, state mortality files Exposure assessment method: questionnaire, interview (direct or next-of-kin)	NHL	Any glyphosate exposure	36	2.1 (1.1–4)	Age, study area, other pesticides	Both logistic regression and hierarchical regression were used in data analysis, the latter providing more conservative estimates [Strengths: increased power when compared with other studies, population-based, and conducted in farming areas. Advanced analytical methods to account for multiple exposures] Included participants from Cantor et al. (1992), Zahm et al. (1990), Hoar et al. (1986), and Brown et al. (1990)

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lee *et al.* (2004a) Iowa, Minnesota and Nebraska, USA 1980–1986	Cases: 872 (response rate, NR); diagnosed with NHL from 1980 to 1986 Controls: 2381 (response rate, NR); frequency-matched controls Exposure assessment method: questionnaire; information on use of pesticides and history of asthma was based on interviews	NHL	Exposed to glyphosate – non-asthmatics	53	1.4 (0.98–2.1)	Age, vital status, state	177 participants (45 NHL cases, 132 controls) reported having been told by their doctor that they had asthma
			Exposed to glyphosate – asthmatics	6	1.2 (0.4–3.3)		
Canada							
McDuffie *et al.* (2001) Canada 1991–1994	Cases: 517 (response rate, 67.1%), from cancer registries and hospitals Controls: 1506 (response rate, 48%); random sample from health insurance and voting records Exposure assessment method: questionnaire, some administered by telephone, some by post	NHL	Exposed to glyphosate	51	1.2 (0.83–1.74)	Age, province of residence	Cross-Canada study [Strengths: large population based study. Limitations: no quantitative exposure data. Exposure assessment by questionnaire. Relatively low participation]
			Unexposed	464	1		
			> 0 and ≤ 2 days	28	1.0 (0.63–1.57)		
			> 2 days	23	2.12 (1.2–3.73)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Karunanayake et al. (2012) Six provinces in Canada (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia) 1991–1994	Incident cases: 316 (response rate, 68.4%); men aged ≥ 19 years; ascertained from provincial cancer registries, except in Quebec (hospital ascertainment) Controls: 1506 (response rate, 48%); matched by age ± 2 years to be comparable with the age distribution of the entire case group (HL, NHL, MM, and STS) within each province of residence. Potential controls (men aged ≥ 19 years) selected at random within age constraints from the provincial health insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario), or voters' lists (British Columbia) Exposure assessment method: questionnaire; stage 1 used a self-administered postal questionnaire, and in stage 2 detailed pesticide exposure information was collected by telephone interview	HL (ICDO2 included nodular sclerosis (M9656/3; M9663/3; M9664/3; M9665/3; M9666/3; M9667/3), lymphocytic predominance (M9651/3; M9657/3; M9658/3; M9659/3), mixed cellularity (M9652/3), lymphocytic depletion (M9653/3; M9654/3), miscellaneous (other M9650-M9669 codes for HL)	Glyphosate-based formulation	38	1.14 (0.74–1.76)	Age group, province of residence	Cross Canada study Based on the statistical analysis of pilot study data, it was decided that the most efficient definition of pesticide exposure was a cumulative exposure ≥ 10 hours/year to any combination of pesticides. This discriminated (a) between incidental, bystander, and environmental exposure vs more intensive exposure, and (b) between cases and controls [Strengths: large study. Limitations: low response rates]
			Glyphosate-based formulation	38	0.99 (0.62–1.56)	Age group, province of residence, medical history	

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kachuri et al. (2013) Six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario and Quebec) 1991–1994	Cases: 342 (response rate, 58%); men aged ≥ 19 years diagnosed between 1991 and 1994 were ascertained from provincial cancer registries except in Quebec, where ascertained from hospitals Controls: 1357 (response rate, 48%); men aged ≥ 19 years selected randomly using provincial health insurance records, random digit dialling, or voters' lists, frequency-matched to cases by age (±2 years) and province of residence Exposure assessment method: questionnaire	Multiple myeloma	Glyphosate use	32	1.19 (0.76–1.87)	Age, province of residence, use of a proxy respondent, smoking status, medical variables, family history of cancer	Cross-Canada study [Strengths: population-based case–control study. Limitations: relatively low response rates]
			Use of glyphosate (> 0 and ≤ 2 days per year)	15	0.72 (0.39–1.32)		
			Use of glyphosate (> 2 days per year)	12	2.04 (0.98–4.23)		
Sweden							
Nordström et al. (1998) Sweden 1987–1992	Cases: 111 (response rate, 91%); 121 HCL cases in men identified from Swedish cancer registry Controls: 400 (response rate, 83%); 484 (four controls/case) matched for age and county; national population registry Exposure assessment method: questionnaire; considered exposed if minimum exposure of 1 working day (8 h) and an induction period of at least 1 year	HCL	Exposed to glyphosate	4	3.1 (0.8–12)	Age	Overlaps with Hardell et al. (2002). HCL is a subtype of NHL [Strengths: population-based case–control study. Limitations: Limited power. There was no adjustment for other exposures]

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hardell & Eriksson (1999) Northern and middle Sweden 1987–1990	Cases: 404 (192 deceased) (response rate, 91%); regional cancer registries Controls: 741 (response rate, 84%); live controls matched for age and county were recruited from the national population registry, and deceased cases matched for age and year of death were identified from the national registry for causes of death Exposure assessment method: questionnaire	NHL (ICD-9 200 and 202)	Ever glyphosate – univariate	4	2.3 (0.4–13)	Not specified in the multivariable analysis	Overlaps with Hardell et al. (2002) [Strengths: population-based study. Limitations: few subjects were exposed to glyphosate and the study had limited power. Analyses were "multivariate" but covariates were not specified]
			Ever glyphosate – multivariate	NR	5.8 (0.6–54)		
Hardell et al. (2002) Sweden; four Northern counties and three counties in mid Sweden 1987–1992	Cases: 515 (response rate, 91% in both studies); Swedish cancer registry Controls: 1141 (response rates, 84% and 83%%); national population registry Exposure assessment method: questionnaire	NHL and HCL	Ever glyphosate exposure (univariate)	8	3.04 (1.08–8.5)	Age, county, study site, vital status, other pesticides in the multivariate analysis	Overlaps with Nordström et al. (1998) and Hardell & Eriksson (1999), [Strengths: large population-based study. Limitations: limited power for glyphosate exposure]
			Ever glyphosate exposure (multivariate)	8	1.85 (0.55–6.2)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Eriksson *et al.* (2008) Sweden. Four health service areas (Lund, Linkoping, Orebro and Umea) 1999–2002	Cases: 910 (response rate, 91%); incident NHL cases were enrolled from university hospitals Controls: 1016 (response rate, 92%); national population registry Exposure assessment method: questionnaire	NHL	Any glyphosate	29	2.02 (1.1–3.71)	Age, sex, year of enrolment	[Strengths: population-based case-control. Limitations: limited power for glyphosate] * Exposure to other pesticides (e.g. MPCA) controlled in the analysis
			Any glyphosate*	29	1.51 (0.77–2.94)		
			≤ 10 days per year use	12	1.69 (0.7–4.07)		
			> 10 days per year use	17	2.36 (1.04–5.37)		
		NHL	1–10 yrs	NR	1.11 (0.24–5.08)		
			> 10 yrs	NR	2.26 (1.16–4.4)		
		B-cell lymphoma	Exposure to glyphosate	NR	1.87 (0.998–3.51)		
		Lymphocytic lymphoma/B-CLL	Exposure to glyphosate	NR	3.35 (1.42–7.89)		
		Diffuse large B-cell lymphoma	Exposure to glyphosate	NR	1.22 (0.44–3.35)		
		Follicular, grade I–III	Exposure to glyphosate	NR	1.89 (0.62–5.79)		
		Other specified B-cell lymphoma	Exposure to glyphosate	NR	1.63 (0.53–4.96)		
		Unspecified B-cell lymphoma	Exposure to glyphosate	NR	1.47 (0.33–6.61)		
		T-cell lymphoma	Exposure to glyphosate	NR	2.29 (0.51–10.4)		
		Unspecified NHL	Exposure to glyphosate	NR	5.63 (1.44–22)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Other studies in Europe							
Orsi *et al.* (2009) France 2000–2004	Cases: 491 (response rate, 95.7%); cases (244 NHL; 87 HL; 104 LPSs; 56 MM) were recruited from main hospitals of the French cities of Brest, Caen, Nantes, Lille, Toulouse and Bordeaux, aged 20–75 years; ALL cases excluded Controls: 456 (response rate, 91.2%); matched on age and sex, recruited in the same hospitals as the cases, mainly in orthopaedic and rheumatological departments and residing in the hospital's catchment area Exposure assessment method: questionnaire	NHL	Any glyphosate exposure	12	1.0 (0.5–2.2)	Age, centre, socioeconomic category (blue/ white collar)	[Limitations: limited power for glyphosate]
		HL	Any exposure to glyphosate	6	1.7 (0.6–5)		
		LPS	Any exposure to glyphosate	4	0.6 (0.2–2.1)		
		MM	Any exposure to glyphosate	5	2.4 (0.8–7.3)		
		All lymphoid neoplasms	Any exposure to glyphosate	27	1.2 (0.6–2.1)		
		NHL, diffuse large cell lymphoma	Occupational use of glyphosate	5	1.0 (0.3–2.7)		
		NHL, follicular lymphoma	Occupational exposure to glyphosate	3	1.4 (0.4–5.2)		
		LPS/CLL	Occupational exposure to glyphosate	2	0.4 (0.1–1.8)		
		LPS/HCL	Occupational exposure to glyphosate	2	1.8 (0.3–9.3)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cocco et al. (2013) Czech Republic, France, Germany, Italy, Ireland and Spain 1998–2004	Cases: 2348 (response rate, 88%); cases were all consecutive adult patients first diagnosed with lymphoma during the study period, resident in the referral area of the participating centres Controls: 2462 (response rate, 81% hospital; 52% population); controls from Germany and Italy were randomly selected by sampling from the general population and matched to cases on sex, 5-year age-group, and residence area. The rest of the centres used matched hospital controls, excluding diagnoses of cancer, infectious diseases and immunodeficiency diseases Exposure assessment method: questionnaire; support of a crop-exposure matrix to supplement the available information, industrial hygienists and occupational experts in each participating centre reviewed the general questionnaires and job modules to assess exposure to pesticides	B-cell lymphoma	Occupational exposure to glyphosate	4	3.1 (0.6–17.1)	Age, sex, education, centre	EPILYMPH case-control study in six European countries

ALL, acute lymphocytic leukaemia; B-CLL, chronic lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; HCL, hairy cell leukaemia; HL, Hodgkin lymphoma; LPS, lymphoproliferative syndrome; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; ref., reference; STS, soft tissue sarcoma population-based, and conducted in farming areas. Potential confounding from multiple exposures was accounted for in the analysis.]

Using the data set of the pooled population-based case–control studies in Iowa, Minnesota, and Nebraska, USA, Lee *et al.* (2004a) investigated whether asthma acts as an effect modifier of the association between pesticide exposure and NHL. The study included 872 cases diagnosed with NHL from 1980 to 1986 and 2381 frequency-matched controls. Information on use of pesticides and history of asthma was based on interviews. A total of 177 subjects (45 cases, 132 controls) reported having been told by their doctor that they had asthma. Subjects with a history of asthma had a non-significantly lower risk of NHL than non-asthmatics, and there was no main effect of pesticide exposure. In general, asthmatics tended to have larger odds ratios associated with exposure to pesticides than non-asthmatics. There was no indication of effect modification: the odds ratio associated with glyphosate use was 1.4 (95% CI, 0.98–2.1; 53 exposed cases) among non-asthmatics and 1.2 (95% CI, 0.4–3.3; 6 exposed cases) for asthmatics, when compared with non-asthmatic non-exposed farmers). [This analysis overlapped with that of De Roos *et al.* (2003).]

(b) *The cross-Canada case–control study*

McDuffie *et al.* (2001) studied the associations between exposure to specific pesticides and NHL in a multicentre population-based study with 517 cases and 1506 controls among men of six Canadian provinces (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). Odds ratios of 1.26 (95% CI, 0.87–1.80; 51 exposed cases; adjusted for age and province) and 1.20 (95% CI, 0.83–1.74, adjusted for age, province, high-risk exposures) were observed for exposure to glyphosate. In an analysis by frequency of exposure to glyphosate, participants with > 2 days of exposure per year had an odds ratio of 2.12 (95% CI, 1.20–3.73, 23 exposed cases) compared with those with some, but ≤ 2 days of exposure. [The study was large, but had relatively low participation rates.]

Kachuri *et al.* (2013) investigated the association between lifetime use of pesticides and multiple myeloma in a population-based case–control study among men in six Canadian provinces between 1991 and 1994 (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). Data from 342 cases of multiple myeloma and 1357 controls were obtained for ever-use of pesticides, number of pesticides used, and days per year of pesticide use. The odds ratios were adjusted for age, province of residence, type of respondent, smoking and medical history. The odds ratio for ever-use of glyphosate was 1.19 (95% CI, 0.76–1.87; 32 cases). When the analysis was conducted by level of exposure, no association was found for light users (≤ 2 days per year) of glyphosate (OR, 0.72; 95% CI, 0.39–1.32; 15 exposed cases) while the odds ratio in heavier users (> 2 days per year) was 2.04 (95% CI, 0.98–4.23; 12 exposed cases). [The study had relatively low response rates. Multiple myeloma is now considered a subtype of NHL.]

(c) *Case–control studies in Sweden*

Nordström *et al.* (1998) conducted a population case–control study in Sweden on hairy cell leukaemia (considered to be a subgroup of NHL). The study included 121 cases in men and 484 controls matched for age and sex. An age-adjusted odds ratio of 3.1 (95% CI, 0.8–12; 4 exposed cases) was observed for exposure to glyphosate. [This study had limited power to detect an effect, and there was no adjustment for other exposures.]

Hardell & Eriksson (1999) reported the results of a population-based case–control study on the incidence of NHL in men associated with pesticide exposure in four northern counties in Sweden. Exposure data was collected by questionnaire (also supplemented by telephone interviews) from 404 cases (192 deceased) and 741 controls (matched by age, sex, county, and vital status). Increased risks of NHL were found for subjects exposed to herbicides and fungicides. The odds ratio for ever-use of glyphosate was 2.3 (95% CI, 0.4–13; 4 exposed cases) in a univariate analysis, and 5.8 (95% CI, 0.6–54) in a multivariable analysis. [The exposure frequency was low for glyphosate, and the study had limited power to detect an effect. The variables included in the multivariate analysis were not specified. This study may have overlapped partially with those of Hardell *et al.* (2002).]

Hardell *et al.* (2002) conducted a pooled analysis of two case–control studies, one on NHL (already reported in Hardell & Eriksson, 1999) and another on hairy cell leukaemia, a subtype of NHL (already reported by Nordström *et al.*, 1998). The pooled analysis of NHL and hairy cell leukaemia was based on 515 cases and 1141 controls. Increased risk was found for exposure to glyphosate (OR, 3.04; 95% CI, 1.08–8.52; 8 exposed cases) in the univariate analysis, but the odds ratio decreased to 1.85 (95% CI, 0.55–6.20) when study, study area, and vital status were considered in a multivariate analysis. [The exposure frequency was low for glyphosate and the study had limited power. This study partially overlapped with those of Hardell & Eriksson (1999) and Nordström *et al.* (1998).]

Eriksson *et al.* (2008) reported the results of a population based case–control study of exposure to pesticides as a risk factor for NHL. Men and women aged 18–74 years living in Sweden were included from 1 December 1999 to 30 April 2002. Incident cases of NHL were enrolled from university hospitals in Lund, Linköping, Örebro, and Umeå. Controls (matched by age and sex) were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total, 910 (91%) cases and 1016 (92%) controls participated. Multivariable models included agents with statistically significant increased odds ratios (MCPA, 2-methyl-4-chlorophenoxyacetic acid), or with an odds ratio of > 1.50 and at least 10 exposed subjects (2,4,5-T and/or 2,4-D; mercurial seed dressing, arsenic, creosote, tar), age, sex, year of diagnosis or enrolment. The odds ratio for exposure to glyphosate was 2.02 (95% CI, 1.10–3.71) in a univariate analysis, and 1.51 (95% CI, 0.77–2.94) in a multivariable analysis. When exposure for more than 10 days per year was considered, the odds ratio was 2.36 (95% CI, 1.04–5.37). With a latency period of > 10 years, the odds ratio was 2.26 (95% CI, 1.16–4.40). The associations with exposure to glyphosate were reported also for lymphoma subtypes, and elevated odds ratios were reported for most of the cancer forms, including B-cell lymphoma (OR, 1.87; 95% CI, 0.998–3.51) and the subcategory of small lymphocytic lymphoma/chronic lymphocytic leukaemia (OR, 3.35; 95% CI, 1.42–7.89; [not adjusted for other pesticides]). [This was a large study; there was possible confounding from use of other pesticides including MCPA, but this was considered in the analysis.]

(d) Other case–control studies in Europe

Orsi *et al.* (2009) reported the results of a hospital-based case–control study conducted in six centres in France between 2000 and 2004. Incident cases with a diagnosis of lymphoid neoplasm aged 20–75 years and controls of the same age and sex as the cases were recruited in the same hospital, mainly in the orthopaedic and rheumatological departments during the same period. [The Working Group noted that the age of case eligibility was given in the publication as 20–75 years in the materials and methods section, but as 18–75 years in the abstract.] Exposures to pesticides were evaluated through specific interviews and case-by-case expert reviews. The analyses included 491 cases (244 cases of NHL, 87 cases of Hodgkin lymphoma), 104 of lymphoproliferative syndrome, and 56 cases of multiple myeloma), and 456 age- and sex-matched controls. Positive associations between some subtypes and occupational exposure to several pesticides were noted. The odds ratios associated with any exposure to glyphosate were 1.2 (95% CI, 0.6–2.1; 27 exposed cases) for all lymphoid neoplasms combined, 1.0 (95% CI, 0.5–2.2; 12 exposed cases) for NHL, 0.6 (95% CI, 0.2–2.1; 4 exposed cases) for lymphoproliferative syndrome, 2.4 (95% CI, 0.8–7.3) for multiple myeloma, and 1.7 (95% CI, 0.6–5.0; 6 exposed cases) for Hodgkin lymphoma, after adjusting for age, centre, and socioeconomic category ("blue/white collar").

Cocco *et al.* (2013) reported the results of a pooled analysis of case–control studies conducted in six European countries in 1998–2004 (EPILYMPH, Czech Republic, France, Germany, Ireland, Italy, and Spain) to investigate the role of occupational exposure to specific groups of chemicals in the etiology of lymphoma overall, B-cell lymphoma, and its most prevalent subtypes. A total of 2348 incident cases of lymphoma and 2462 controls were recruited. Controls from Germany and Italy were randomly selected by sampling from the general population, while the rest of the centres used matched hospital controls. Overall, the participation rate was 88% for cases, 81% for hospital controls, and 52% for population controls. An occupational history was collected with farm work-specific questions on type of crop, farm size, pests being treated, type and schedule of pesticide use. In each study centre, industrial hygienists and occupational experts assessed exposure to specific groups of pesticides and individual compounds with the aid of agronomists. [Therefore any exposure misclassification would be non-differential.] Analyses were conducted for lymphoma and the most prevalent lymphoma subtypes adjusting for age, sex, education, and centre. Lymphoma overall, and B-cell lymphoma were not associated with any class of the investigated pesticides, while the risk of chronic lymphocytic leukaemia was elevated among those ever exposed to inorganic and organic pesticides. Only for a few individual agrochemicals was there a sizeable number of study subjects to conduct a meaningful analysis, and the odds ratio for exposure to glyphosate and B-cell lymphoma was 3.1 (95% CI, 0.6–17.1; 4 exposed cases and 2 exposed controls). [The study had a very limited power to assess the effects of glyphosate on risk of NHL.]

2.2.2 Other haematopoietic cancers

Orsi *et al.* (2009) also reported results for Hodgkin lymphoma (see Section 2.2.1).

Karunanayake *et al.* (2012) conducted a case–control study of Hodgkin lymphoma among white men, aged 19 years or older, in six regions of Canada (see the Malathion *Monograph*, Section 2.0, for a detailed description of this study). The analysis included 316 cases and 1506 age-matched (± 2 years) controls. Based on 38 cases exposed to glyphosate, the odds ratios were 1.14 (95% CI, 0.74–1.76) adjusted for age and province, and 0.99 (95% CI, 0.62–1.56) when additionally adjusted for medical history variables.

Brown *et al.* (1990) evaluated exposure to carcinogens in an agricultural setting and the relationship with leukaemia in a population-based case–control interview study in Iowa and Minnesota, USA, including 578 white men with leukaemia and 1245 controls. The exposure assessment was done with a personal interview of the living subjects or the next-of-kin. Farmers had a higher risk of all leukaemias compared with non-farmers, and associations were found for exposure to specific animal insecticides, including the organophosphates crotoxyphos, dichlorvos, famphur, pyrethrins, and methoxychlor. The odds ratio for glyphosate was 0.9 (95% CI, 0.5–1.6; 15 exposed cases; adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures). [This was a large study in an agricultural setting, but had limited power for studying the effects of glyphosate use.]

2.3 Case–control studies on other cancer sites

2.3.1 Cancer of the oesophagus and stomach

Lee *et al.* (2004b) evaluated the risk of adenocarcinomas of the oesophagus and stomach associated with farming and agricultural pesticide use. The population-based case–control study was conducted in eastern Nebraska, USA. Subjects of both sexes diagnosed with adenocarcinoma of the stomach (*n* = 170) or oesophagus (*n* = 137) between 1988 and 1993 were enrolled. Controls (*n* = 502) were randomly selected from the population registry of the same geographical area. The response rates were 79% for cancer of the stomach, 88% for cancer of the oesophagus, and 83% for controls. Adjusted odds ratios were estimated for use of individual and chemical classes of insecticides and herbicides, with non-farmers as the reference category. No association was found with farming or ever-use of insecticides or herbicides, or with individual pesticides. For ever-use of glyphosate, the odds ratio was 0.8 (95% CI, 0.4–1.4; 12 exposed cases) for cancer of the stomach, and 0.7 (95% CI, 0.3–1.4; 12 exposed cases) for oesophageal cancer. [The study was conducted in a farming area, but the power to detect an effect of glyphosate use was limited.]

2.3.2 Cancer of the brain

Ruder *et al.* (2004) conducted a case–control study on glioma among nonmetropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin in the Upper Midwest Health Study, USA. The study included 457 cases of glioma and 648 population-based controls, all adult men. Exposure assessment was done with interviews of the subject or the relatives. The response rates were 93% and 70% for cases and controls, respectively. No association were found with any of the pesticides assessed, including glyphosate. [Glyphosate use was assessed, but specific results were not presented.]

Carreón *et al.* (2005) evaluated the effects of rural exposures to pesticides on risk of glioma among women aged 18–80 years who were nonmetropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin in the Upper Midwest Health Study, USA. A total of 341 cases of glioma and 528 controls were enrolled. A personal interview was carried out for exposure assessment. The response rates were 90% and 72%, respectively. After adjusting for age, age group, education, and farm residence, no association with glioma was observed for exposure to several pesticide classes or individual pesticides. There was a reduced risk for glyphosate (OR, 0.7; 95% CI, 0.4–1.3; 18 exposed cases). These results were not affected by the exclusion of proxy respondents (43% of cases, 2% of controls).

Lee *et al.* (2005) evaluated the association between farming and agricultural pesticide use and risk of adult glioma in a population-based case–control study in eastern Nebraska, USA. Cases of glioma were in men and women (*n* = 251) and were compared with population controls from a previous study (*n* = 498). A telephone interview was conducted for 89% of the cases and 83% of the controls. Adjusted odds ratios for farming and for use of individual and chemical classes of insecticides and herbicides were calculated using non-farmers as the reference category. Among men, ever living or working on a farm and duration of farming were associated with significantly increased risks of glioma, but the positive findings were limited to proxy respondents. Among women, there were no positive associations with farming activities among self or proxy respondents. Some specific pesticide families and individual pesticides were associated with significantly increased risks among male farmers, but most of the positive associations were limited to proxy respondents. There was a non-significant excess risk with glyphosate use for the overall group (OR, 1.5; 95% CI, 0.7–3.1; 17 exposed cases), but there was inconsistency between observations for self-respondents (OR, 0.4; 95% CI, 0.1–1.6) and observations for proxy respondents (OR, 3.1; 95% CI, 1.2–8.2). [The study had limited power to detect an effect of glyphosate use, and the inconsistencies for self and proxy respondents made the results difficult to interpret.]

2.3.3 Soft tissue sarcoma

Pahwa *et al.* (2011) reported the results of the soft tissue sarcoma component of the cross-Canada study in relation to specific pesticides, including 357 cases of soft tissue sarcoma and 1506 population controls from 1991–1994. The fully adjusted odds ratio for glyphosate use was 0.90 (95% CI, 0.58–1.40).

2.3.4 Cancer of the prostate

Band *et al.* (2011) report results of a case–control study including 1516 patients with cancer of the prostate (ascertained by the cancer registry of British Columbia, Canada, for 1983–90) and 4994 age-matched controls with cancers at all other cancer sites excluding lung and unknown primary site. Agricultural exposures were assessed by job-exposure matrix. A total of 60 cases were exposed to glyphosate (adjusted OR, 1.36; 95% CI, 0.83–2.25).

2.3.5 Childhood cancer

Parental exposure to pesticides, including glyphosate, was assessed in a population-based case–control study of childhood leukaemia in Costa Rica (Monge *et al.*, 2007). However, associations of childhood cancer with glyphosate were reported only for an "other pesticides" category that also included paraquat, chlorothalonil, and other chemicals. [Because glyphosate was not specifically assessed, this study was not evaluated by the Working Group.]

2.4. Meta-analyses

Schinasi & Leon (2014) conducted a systematic review and meta-analysis of NHL and occupational exposure to agricultural pesticides, including glyphosate. The meta-analysis for glyphosate included six studies (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; De Roos *et al.*, 2003; 2005a; Eriksson *et al.*, 2008; Orsi *et al.*, 2009) and yielded a meta risk-ratio of 1.5 (95% CI, 1.1–2.0). [The Working Group noted that the most fully adjusted risk estimates from the articles by Hardell *et al.* (2002) and Eriksson *et al.* (2008) were not used in this analysis. After considering the adjusted estimates of the two Swedish studies in the meta-analysis, the Working Group estimated a meta risk-ratio of 1.3 (95% CI, 1.03–1.65), I^2 = 0%, *P* for heterogeneity 0.589.]

3. Cancer in Experimental Animals

3.1 Mouse

See Table 3.1

3.1.1 Dietary administration

Groups of 50 male and 50 female CD-1 mice [age not reported] were given diets containing glyphosate (purity, 99.7%) at a concentration of 0, 1000, 5000, or 30 000 ppm, ad libitum, for 24 months. There was no treatment-related effect on body weight in male and female mice at the lowest or intermediate dose. There was a consistent decrease in body weight in the male and female mice at the highest dose compared with controls. Survival in all dose groups was similar to that of controls. There was a positive trend (*P* = 0.016, trend test; see EPA, 1985b) in the incidence of renal tubule adenoma in dosed male mice: 0/49, 0/49, 1/50 (2%), 3/50 (6%). [The Working Group noted that renal tubule adenoma is a rare tumour in CD-1 mice.] No data on tumours of the kidney

Table 3.1 Studies of carcinogenicity with glyphosate in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, CD-1 (M, F) 24 mo EPA (1985a, b, 1986, 1991a)	Diet containing glyphosate (technical grade; purity, 99.7%) at concentrations of 0, 1000, 5000, or 30 000 ppm, ad libitum, for 24 mo 50 M and 50 F/group [age, NR]	*Males* Renal tubule adenoma: 0/49, 0/49, 1/50 (2%), 3/50 (6%) *Females* No data provided on the kidney	*P* for trend = 0.016; see Comments	No information was provided on renal tubule adenomas in female mice, or on statistical analyses of tumour data EPA recommended that additional renal sections be cut and evaluated from all control and treated male mice. The pathology report for these additional sections (EPA, 1985b) showed the same incidence of renal tubule adenomas as originally reported, with no significant difference in incidence when comparing control and treated groups; however, the test for linear trend in proportions resulted in *P* = 0.016 EPA (1986) convened a PWG and requested additional pathological and statistical information on kidney tumours observed in male mice treated with glyphosate
		Report from the PWG of the EPA (1986): *Males* Renal tubule adenoma: 1/49 (2%), 0/49, 0/50, 1/50 (2%)	[NS]	
		Renal tubule carcinoma: 0/49, 0/49, 1/50 (2%), 2/50 (4%)	[*P* = 0.037; Cochran–Armitage trend test]	
		Renal tubule adenoma or carcinoma (combined): 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%)	[*P* = 0.034; Cochran–Armitage trend test]	
Mouse, CD-1 (M, F) 104 wk JMPR (2006)	Diet containing glyphosate (purity, 98.6%) at doses of 0, 100, 300, 1000 mg/kg bw, ad libitum, for 104 wk 50 M and 50 F/group [age, NR]	*Males* Haemangiosarcoma: 0/50, 0/50, 0/50, 4/50 (8%)	[*P* < 0.001; Cochran–Armitage trend test]	
		Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue: 0/50, 2/50 (4%), 0/50, 2/50 (4%)	NS	
		Females Haemangiosarcoma: 0/50, 2/50 (4%), 0/50, 1/50 (2%)	NS	
		Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue: 0/50, 3/50 (6%), 3/50 (6%), 1/50 (2%)	NS	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, Swiss (M) 32 wk George et al. (2010)	Initiation–promotion study Skin application of glyphosate-based formulation (glyphosate, 41%; POEA, ~15%) (referred to as "glyphosate") dissolved in 50% ethanol; DMBA dissolved in 50% ethanol, and TPA dissolved in 50% acetone, used in the groups described below 20 M/group	Skin tumours [called "papillomas" by the authors, following gross examination only]		Short duration of treatment, no solvent controls, and lack of any histopathological evaluation Age at start, NR (mice weighed 12–15 g bw) [The Working Group concluded this was an inadequate study for the evaluation of glyphosate]
	Group I: untreated control (no treatment)	Group I: 0/20		
	Group II: glyphosate only: 25 mg/kg bw topically, 3 × /wk, for 32 wk	Group II: 0/20		
	Group III: single topical application of DMBA, 52 µg/mouse, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group III: 20/20*, 7.8 ± 1.1	*$P < 0.05$ vs groups VI and VII	
	Group IV: single topical application of glyphosate, 25 mg/kg bw, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group I: 0/20		
	Group V: 3 × /wk topical application of glyphosate, 25 mg/kg bw, for 3 wk, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group V: 0/20		
	Group VI: single topical application of DMBA, 52 µg/mouse	Group VI: 0/20		
	Group VII: topical application of TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group VII: 0/20		
	Group VIII: single topical application of DMBA, 52 µg/mouse, followed 1 wk later by topical treatment with glyphosate, 25 mg/kg bw, 3 × /wk, for 32 wk	Group VIII: 8/20*, 2.8 ± 0.9	*$P < 0.05$ vs group VI	

bw, body weight; DMBA, 7,12-dimethylbenz[*a*]anthracene; EPA, United States Environmental Protection Agency; F, female; M, male; mo, month; NR, not reported; NS, not significant; POEA, polyethoxylated tallowamine; PWG, pathology working group; TPA, 12-*O*-tetradecanoyl-phorbol-13-acetate; vs, versus; wk, week; yr, year were provided for female mice. No other tumour sites were identified (EPA, 1985a). Subsequent to its initial report (EPA, 1985a), the United States Environmental Protection Agency (EPA) recommended that additional renal sections be cut and evaluated from all male mice in the control and treated groups. The pathology report for these additional sections (EPA, 1985b) indicated the same incidence of renal tubule adenoma as originally reported, with no significant increase in incidence between the control group and treated groups by pairwise comparison. However, as already reported above, the test for linear trend in proportions resulted in a significance of $P = 0.016$. The EPA (1986) also requested that a pathology working group (PWG) be convened to evaluate the tumours of the kidney observed in male mice treated with glyphosate, including the additional renal sections. In this second evaluation, the PWG reported that the incidence of adenoma of the renal tubule was 1/49 (2%), 0/49, 0/50, 1/50 (2%) [not statistically significant]; the incidence of carcinoma of the renal tubule was 0/49, 0/49, 1/50 (2%), 2/50 (4%) [$P = 0.037$, trend test for carcinoma]; and the incidence of adenoma or carcinoma (combined) of the renal tubule was 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%) [$P = 0.034$, trend test for combined]. [The Working Group considered that this second evaluation indicated a significant increase in the incidence of rare tumours, with a dose-related trend, which could be attributed to glyphosate. Chandra & Frith (1994) reported that only 1 out of 725 [0.14%] CD-1 male mice in their historical database had developed renal cell tumours (one carcinoma).]

[The Working Group noted the differences in histopathological diagnosis between pathologists. Proliferative lesions of the renal tubules are typically categorized according to published criteria as hyperplasia, adenoma, or carcinoma. The difference is not trivial, because focal hyperplasia, a potentially preneoplastic lesion, should be carefully differentiated from the regenerative changes of the tubular epithelium. There is a morphological continuum in the development and progression of renal neoplasia. Thus larger masses may exhibit greater heterogeneity in histological growth pattern, and cytologically more pleomorphism and atypia than smaller lesions (Eustis *et al.*, 1994). Of note, a renal tumour confirmed by the PWG after re-evaluation of the original slides (EPA, 1986), had not been seen in the re-sectioned kidney slides (EPA, 1985b). This may be related to the growth of tumour that – in contrast to tumours in other organs – is not spherical but elliptical because of the potential expansion in tubules. In addition, the concept of tubular expansion without compression of adjacent parenchyma may be at the basis of the discrepancy between the first (EPA, 1985a, b) and second evaluation (EPA, 1986).]

In another study reported to the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), groups of 50 male and 50 female CD-1 mice [age at start not reported] were given diets containing glyphosate (purity, 98.6%) at a concentration that was adjusted weekly for the first 13 weeks and every 4 weeks thereafter to give doses of 0, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 weeks (JMPR, 2006). There was no treatment-related effect on body weight or survival in any of the dosed groups. There was an increase in the incidence of haemangiosarcoma in males – 0/50, 0/50, 0/50, 4/50 (8%) [$P < 0.001$, Cochran–Armitage trend test], and in females – 0/50, 2/50 (4%), 0/50, 1/50 (2%) [not statistically significant], and an increase in the incidence of histiocytic sarcoma in the lymphoreticular/haemopoietic tissue in males – 0/50, 2/50 (4%), 0/50, 2/50 (4%), and in females – 0/50, 3/50 (6%), 3/50 (6%), 1/50 (2%) [not statistically significant for males or females]. [The Working Group considered that this study was adequately reported.]

3.1.2 Initiation–promotion

Groups of 20 male Swiss mice [age at start not reported; body weight, 12–15g] were given a glyphosate-based formulation (glyphosate, 41%; polyethoxylated tallowamine, ~15%) (referred to as glyphosate in the article) that was dissolved in 50% ethanol and applied onto the shaved back skin (George *et al.*, 2010). Treatment groups were identified as follows:

- Group I – untreated control;
- Group II – glyphosate only (25 mg/kg bw), applied topically three times per week for 32 weeks;
- Group III – single topical application of dimethylbenz[*a*]anthracene (DMBA; in ethanol; 52 µg/mouse), followed 1 week later by 12-*O*-tetradecanoylphorbol-13-acetate (TPA; in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group IV – single topical application of glyphosate (25 mg/kg bw) followed 1 week later by TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group V – glyphosate (25 mg/kg bw) applied topically three times per week for 3 weeks (total of nine applications), followed 1 week later by TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group VI – single topical application of DMBA (in ethanol; 52 µg/mouse);
- Group VII – TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks; and
- Group VIII – single topical application of DMBA (in ethanol; 52 µg/mouse), followed 1 week later by glyphosate (25 mg/kg bw), applied topically three times per week for 32 weeks.

All mice were killed at 32 weeks. Skin tumours were observed only in group III (positive control, DMBA + TPA, 20/20) and group VIII (DMBA + glyphosate, 8/20; $P < 0.05$ versus group VI [DMBA only, 0/20]). No microscopic examination was conducted and tumours were observed "as a minute wart like growth [that the authors called squamous cell papillomas], which progressed during the course of experiment." [The glyphosate formulation tested appeared to be a tumour promoter in this study. The design of the study was poor, with short duration of treatment, no solvent controls, small number of animals, and lack of histopathological examination. The Working Group concluded that this was an inadequate study for the evaluation of glyphosate.]

3.1.3 Review articles

Greim *et al.* (2015) have published a review article containing information on five long-term bioassay feeding studies in mice. Of these studies, one had been submitted for review to the EPA (EPA, 1985a, b, 1986, 1991a), and one to the JMPR (JMPR, 2006); these studies are discussed in Section 3.1.1. The review article reported on an additional three long-term bioassay studies in mice that had not been previously available in the open literature, but had been submitted to various organizations for registration purposes. The review article provided a brief summary of each study and referred to an online data supplement containing the original data on tumour incidence from study reports. The three additional long-term bioassay studies in mice are summarized below. [The Working Group was unable to evaluate these studies, which are not included in Table 3.1 and Section 5.3, because the information provided in the review article and its supplement was insufficient (e.g. information was lacking on statistical methods, choice of doses, body-weight gain, survival data, details of histopathological examination, and/or stability of dosed feed mixture).]

In the first study (identified as Study 12, 1997a), groups of 50 male and 50 female CD-1

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mice [age at start not reported] were given diets containing glyphosate (purity, 94–96%) at a concentration of 0, 1600, 8000, or 40 000 ppm for 18 months. The increase in the incidence of bronchiolo-alveolar adenoma and carcinoma, and of lymphoma, was reported to be not statistically significant in males and females receiving glyphosate. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In the second study (identified as Study 13, 2001), groups of 50 male and 50 female Swiss albino mice [age at start not reported] were given diets containing glyphosate (purity, > 95%) at a concentration of 0 (control), 100, 1000, or 10 000 ppm for 18 months. The authors reported a statistically significant increase in the incidence of malignant lymphoma (not otherwise specified, NOS) in males at the highest dose: 10/50 (20%), 15/50 (30%), 16/50 (32%), 19/50 (38%; $P < 0.05$; pairwise test); and in females at the highest dose: 18/50 (36%), 20/50 (40%), 19/50 (38%), 25/50 (50%; $P < 0.05$; pairwise test). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In the third study (identified as Study 14, 2009a), groups of 51 male and 51 female CD-1 mice [age at start not reported] were given diets containing glyphosate (purity, 94.6–97.6%) at a concentration of 0, 500, 1500, or 5000 ppm for 18 months. Incidences for bronchiolo-alveolar adenoma and carcinoma, malignant lymphoma (NOS), and hepatocellular adenoma and carcinoma in males, and for bronchiolo-alveolar adenoma and carcinoma, malignant lymphoma (NOS) and pituitary adenoma in females, were included in the article. In males, the authors reported that there was a significant positive trend [statistical test not specified] in the incidence of bronchiolo-alveolar carcinoma (5/51, 5/51, 7/51, 11/51) and of malignant lymphoma (0/51, 1/51, 2/51, 5/51). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

3.2 Rat

See Table 3.2

3.2.1 Drinking-water

Groups of 10 male and 10 female Sprague-Dawley rats (age, 5 weeks) were given drinking-water containing a glyphosate-based formulation at a dose of 0 (control), 1.1 × 10^{-8}% (50×10^{-5} mg/L), 0.09% (400 mg/L) or 0.5% (2.25 × 10^3 mg/L), ad libitum, for 24 months (Séralini *et al.*, 2014). [The study reported is a life-long toxicology study on a glyphosate-based formulation and on genetically modified NK603 maize, which the authors stated was designed as a full study of long-term toxicity and not a study of carcinogenicity. No information was provided on the identity or concentration of other chemicals contained in this formulation.] Survival was similar in treated and control rats. [No data on body weight were provided.] In female rats, there was an almost twofold increase in the incidence of tumours of the mammary gland (mainly fibroadenoma and adenocarcinoma) in animals exposed to the glyphosate-based formulation only versus control animals: control, 5/10 (50%); lowest dose, 9/10 (90%); intermediate dose, 10/10 (100%) [$P < 0.05$; Fisher exact test]; highest dose, 9/10 (90%). [The Working Group concluded that this study conducted on a glyphosate-based formulation was inadequate for evaluation because the number of animals per group was small, the histopathological description of tumours was poor, and incidences of tumours for individual animals were not provided.]

In another study with drinking-water, Chruscielska *et al.* (2000) gave groups of 55 male and 55 female Wistar rats (age, 6–7 weeks) drinking-water containing an ammonium salt of glyphosate as a 13.85% solution [purity of glyphosate, not reported] that was used to make aqueous solutions of 0 (control), 300, 900, and 2700 mg/L, for 24 months [details on the dosing regimen were not reported]. The authors reported that survival and body-weight gain were similar in treated and control animals. No significant increase in tumour incidence was reported in any of the treated groups. [The Working Group noted the limited information provided on dosing regimen, histopathological examination method, and tumour incidences.]

3.2.2 Dietary administration

The JMPR report included information on a 1-year feeding study in which groups of 24 male and 24 female Wistar-Alpk:APfSD rats [age at start not reported] were given diets containing glyphosate (purity, 95.6%) at a concentration of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 1 year (JMPR, 2006). There was a treatment-related decrease in body-weight gain at the two highest doses (significant at 20 000 ppm for both sexes, and at 8000 ppm only in females). There was no treatment-related decrease in survival. No significant increase in tumour incidence was observed in any of the treated groups. [The Working Group noted the short duration of exposure.]

The JMPR report also included information on a 104-week feeding study in which groups of 50 male and 50 female Sprague-Dawley rats [age at start not reported] were given diets containing glyphosate (purity, 98.7–98.9%) at a concentration that was adjusted to provide doses of 0, 10, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 weeks (JMPR, 2006). There was a treatment-related decrease in body-weight gain in males and females at the highest dose. There was no significant treatment-related decrease in survival or increase in tumour incidence in any of the treated groups.

Information was also included in the JMPR report on a 24-month feeding study in which groups of 52 male and 52 female Wistar-Alpk:APfSD rats [age at start not reported] were given diets containing glyphosate (purity, 97.6%) at a concentration of 0, 2000, 6000, or 20 000 ppm, ad libitum, for 24 months (JMPR, 2006). There was a treatment-related decrease in body-weight gain in males and females at the highest dose, and a corresponding significant increase in survival in males. No significant increase in tumour incidence was observed in any of the treated groups.

The EPA (1991a, b, c, d) provided information on a long-term study in which groups of 60 male and 60 female Sprague-Dawley rats (age, 8 weeks) were given diets containing glyphosate (technical grade; purity, 96.5%) at a concentration of 0 ppm, 2000 ppm, 8000 ppm, or 20 000 ppm, ad libitum, for 24 months. Ten animals per group were killed after 12 months. There was no compound-related effect on survival, and no statistically significant decreases in body-weight gain in male rats. In females at the highest dose, body-weight gain was significantly decreased, starting on day 51. In males at the lowest dose, there was a statistically significant increase in the incidence of pancreatic islet cell adenoma compared with controls: 8/57 (14%) versus 1/58 (2%), $P \leq 0.05$ (Fisher exact test). Additional analyses by the EPA (1991a) (using the Cochran–Armitage trend test and Fisher exact test, and excluding rats that died or were killed before week 55) revealed a statistically significant higher incidence of pancreatic islet cell adenoma in males at the lowest and highest doses compared with controls: lowest dose, 8/45 (18%; $P = 0.018$; pairwise test); intermediate dose, 5/49 (10%); highest dose, 7/48 (15%; $P = 0.042$; pairwise test) versus controls, 1/43 (2%). The range for historical controls for pancreatic islet cell adenoma reported in males at this laboratory was 1.8–8.5%. [The Working Group noted that there was no statistically significant positive trend in the incidence of these tumours, and no apparent progression to carcinoma.] There was also a statistically significant positive trend in the incidence of hepatocellular adenoma in

Table 3.2 Studies of carcinogenicity with glyphosate in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) 24 mo Séralini *et al.* (2014)	Drinking-water containing a glyphosate-based formulation at a concentration of 0 (control), 1.1×10^{-8}% (glyphosate, 5.0×10^{-5} mg/L), 0.09% (glyphosate, 400 mg/L) or 0.5% (glyphosate, 2.25×10^{3} mg/L), ad libitum, for 24 mo 10 M and 10 F/group (age, 5 wk)	*Males* No significant increase in tumour incidence observed in any of the treated groups *Females* Mammary tumours (mainly fibroadenomas and adenocarcinomas): 5/10 (50%), 9/10 (90%), 10/10 (100%)*, 9/10 (90%) Pituitary lesions (hypertrophy, hyperplasia, and adenoma): 6/10 (60%), 8/10 (80%), 7/10 (70%), 7/10 (70%)	 NS *[*P* < 0.05] [NS]	Data are from an in-depth life-long toxicology study on a glyphosate-based formulation and NK603 genetically modified maize; authors stated that the study was designed as a full chronic toxicity and not a carcinogenicity study. No information provided on the identity or concentration of other chemicals contained in this formulation Histopathology poorly described and tumour incidences for individual animals not discussed in detail. Small number of animals per group [The Working Group concluded this was an inadequate study for the evaluation of glyphosate carcinogenicity]
Rat, Wistar (M, F) 24 mo Chruscielska *et al.* (2000)	Drinking-water containing ammonium salt of glyphosate (13.85% solution) [purity of glyphosate, NR] was used to make aqueous solutions of 0, 300, 900, and 2700 mg/L [Details on dosing regimen, NR] 55 M and 55 F/group (age, 6–7 wk)	No significant increase in tumour incidence observed in any of the treated groups	NS	Limited information on dosing regimen, histopathological examination methods, and tumour incidences
Rat, Wistar-Alpk:APfSD (M, F) 1 yr JMPR (2006)	Diet containing glyphosate (purity, 95.6%) at concentrations of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 1 yr 24 M and 24 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	Short duration of exposure
Rat, Sprague-Dawley (M, F) 104 wk JMPR (2006)	Diet containing glyphosate (purity, 98.7–98.9%) at doses of 0, 10, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 wk 50 M and 50 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	
Rat, Wistar-Alpk:APfSD (M, F) 24 mo JMPR (2006)	Diet containing glyphosate (purity, 97.6%) at concentrations of 0, 2000, 6000, or 20 000 ppm, ad libitum, for 2 yr 52 M and 52 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat Sprague-Dawley (M, F) 24 mo EPA (1991a, b, c, d)	Diet containing glyphosate (technical grade; purity, 96.5%) at concentrations of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 24 mo 60 M and 60 F/group (age, 8 wk) 10 rats/group killed after 12 mo	*Males* *Pancreas (islet cell):* Adenoma: 1/58 (2%), 8/57 (14%)*, 5/60 (8%), 7/59 (12%) Carcinoma: 1/58 (2%), 0/57, 0/60, 0/59 Adenoma or carcinoma (combined): 2/58 (3%), 8/57 (14%), 5/60 (8%), 7/59 (12%) *Liver:* Hepatocellular adenoma: 2/60 (3%), 2/60 (3%), 3/60 (6%), 7/60 (12%) Hepatocellular carcinoma: 3/60 (5%), 2/60 (3%), 1/60 (2%), 2/60 (3%) *Females* *Pancreas (islet cell):* Adenoma: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 Carcinoma: 0/60, 0/60, 0/60, 0/59 Adenoma or carcinoma (combined): 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 *Thyroid:* C-cell adenoma: 2/60 (3%), 2/60 (3%), 6/60 (10%), 6/60 (10%) C-cell carcinoma: 0/60, 0/60, 1/60, 0/60	Adenoma, * $P \leq 0.05$ (Fisher exact test with Bonferroni inequality); see comments Adenoma, *P* for trend = 0.016; see comments NS Adenoma, *P* for trend = 0.031; see comments	Historical control range for pancreatic islet cell adenoma reported in males at this laboratory, 1.8–8.5% EPA (1991a) performed additional analyses using the Cochran–Armitage trend test and Fisher exact test, and excluding animals that died or were killed before wk 54–55: *Males* *Pancreas (islet cell):* Adenoma: 1/43 (2%), 8/45 (18%; *P* = 0.018), 5/49 (10%), 7/48 (15%; *P* = 0.042) Carcinoma: 1/43 (2%), 0/45 (0%), 0/49 (0%), 0/48 (0%) Adenoma or carcinoma (combined): 2/43 (5%), 8/45 (18%), 5/49 (10%), 7/48 (15%) [There was no statistically significant positive trend in the incidence of pancreatic tumours, and no apparent progression to carcinoma] *Liver:* Hepatocellular adenoma: 2/44 (5%; *P* for trend = 0.016), 2/45 (4%), 3/49 (6%), 7/48 (15%) Hepatocellular carcinoma: 3/44 (7%); 2/45 (4%), 1/49 (2%), 2/48 (4%) Hepatocellular adenoma or carcinoma (combined): 5/44 (11%), 4/45 (9%), 4/49 (8%), 9/48 (19%) [There was no apparent progression to carcinoma] *Females* *Thyroid:* C-cell adenoma: 2/57 (4%; *P* for trend = 0.031), 2/60 (3%), 6/59 (10%), 6/55 (11%) C-cell carcinoma: 0/57, 0/60, 1/59 (2%), 0/55 C-cell adenoma or carcinoma (combined): 2/57 (4%), 2/60 (3%), 7/59 (12%), 6/55 (11%) [There was no apparent progression to carcinoma]

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat Sprague-Dawley (M, F) Lifetime (up to 26 mo) EPA (1991a, b, c, d)	Diet containing glyphosate (purity, 98.7%) at concentrations of 0 ppm, 30 ppm (3 mg/kg bw per day), 100 ppm (10 mg/kg bw per day), 300 ppm (31 mg/kg bw per day), ad libitum, up to 26 mo 50 M and 50 F/group [age, NR]	*Males* *Pancreas (islet cell):* Adenoma: 0/50 (0%), 5/49* (10%), 2/50 (4%), 2/50 (4%) Carcinoma: 0/50 (0%), 0/49 (0%), 0/50 (0%), 1/50 (2%) Adenoma or carcinoma (combined): 0/50 (0%), 5/49 (10%), 2/50 (4%), 3/50 (6%) *Females* *Pancreas (islet cell):* Adenoma: 2/50 (4%), 1/50 (2%), 1/50 (2%), 0/50 (0%) Carcinoma: 0/50 (0%), 1/50 (2%), 1/50 (2%), 1/50 (2%) Adenoma or carcinoma (combined): 2/50 (10%), 2/50 (2%), 2/50 (74%), 1/50 (2%)	Adenoma, *[$P < 0.05$; Fisher exact test] NS	[There was no statistically significant positive trend in the incidence of pancreatic tumours, and no apparent progression to carcinoma]

bw, body weight; d, day; F, female; M, male; mo, month; NR, not reported; NS, not significant; wk, week; yr, year males (P = 0.016) and of thyroid follicular cell adenoma in females (P = 0.031). [The Working Group noted that there was no apparent progression to carcinoma for either tumour type.]

The EPA (1991a, b, c, d) provided information on another long-term study in which groups of 50 male and 50 female Sprague-Dawley rats [age at start not reported] were given diets containing glyphosate (purity, 98.7%) at a concentration of 0, 30 (3 mg/kg bw per day), 100 (10 mg/kg bw per day), or 300 ppm (31 mg/kg bw per day), ad libitum, for life (up to 26 months). No information was provided on body weight or survival of the study animals. An increase in the incidence of pancreatic islet cell adenoma was reported in males at the lowest dose: controls, 0/50 (0%); lowest dose, 5/49 (10%) [P < 0.05; Fisher exact test]; intermediate dose, 2/50 (4%); highest dose, 2/50 (4%). [The Working Group noted that there was no statistically significant positive dose-related trend in the incidence of these tumours, and no apparent progression to carcinoma.]

3.2.3 Review articles

Greim et al. (2015) have published a review article containing information on nine long-term bioassay feeding studies in rats. Of these studies, two had been submitted for review to the EPA (1991a, b, c, d), two to the JMPR (JMPR, 2006), and one had been published in the openly available scientific literature (Chruscielska et al., 2000); these studies are discussed earlier in Section 3.2. The review article reported on an additional four long-term bioassay studies in rats that had not been previously published, but had been submitted to various organizations for registration purposes. The review article provided a brief summary of each study and referred to an online data supplement containing the original data on tumour incidence from study reports. The four additional long-term bioassay studies in rats are summarized below. [The Working Group did not evaluate these studies, which are not included in Table 3.2 and Section 5.3, because the information provided in the review article and its supplement was insufficient (e.g. information lacking on statistical methods, choice of doses, body-weight gain, survival data, details on histopathological examination and/or stability of dosed feed mixture).]

In one study (identified as Study 4, 1996), groups of 50 male and 50 female Wistar rats [age at start not reported] were given diets containing glyphosate (purity, 96%) at a concentration of 0, 100, 1000, or 10 000 ppm, ad libitum, for 24 months. It was reported that hepatocellular adenomas and hepatocellular carcinomas were found at non-statistically significant incidences in both males and females. There was no significant increase in tumour incidence in the treated groups. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In one study in Sprague-Dawley rats (identified as Study 5, 1997), groups of 50 male and 50 female rats [age at start not reported] were given diets containing glyphosate technical acid [purity not reported] at a concentration of 0, 3000, 15 000, or 25 000 ppm, ad libitum, for 24 months. There was no significant increase in tumour incidence in the treated groups. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In a second study in Sprague Dawley rats (identified as Study 6, 1997b), groups of 50 males and 50 females [age at start not reported] were given diets containing glyphosate (purity, 94.6–97.6%) at a concentration of 0, 3000, 10 000, or 30 000 ppm, ad libitum, for 24 months. Non-significant increases in tumour incidences compared with controls were noted for skin keratoacanthoma in males at the highest dose, and for fibroadenoma of the mammary gland in females at the lowest and intermediate doses. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In another study in male and female Wistar rats (identified as Study 8, 2009b), groups of 51 male and 51 female rats [age at start not reported] were fed diets containing glyphosate (purity, 95.7%) at a concentration of 0, 1500, 5000, or 15 000 ppm, ad libitum, for 24 months. The highest dose was progressively increased to reach 24 000 ppm by week 40. A non-significant increase in tumour incidence was noted for adenocarcinoma of the mammary gland in females at the highest dose (6/51) compared with controls (2/51). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information. The Working Group noted that tumours of the mammary gland had been observed in other studies in rats reviewed for the present *Monograph*.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Introduction

The herbicidal activity of glyphosate is attributed to interference with the production of essential aromatic amino acids (EPA, 1993b). In plants, glyphosate competitively inhibits the activity of enolpyruvylshikimate phosphate synthase, an enzyme that is not present in mammalian cells. Glyphosate is degraded by soil microbes to aminomethylphosphonic acid (AMPA) (see Fig. 4.1), a metabolite that can accumulate in the environment. In mammals, glyphosate is not metabolized efficiently, and is mainly excreted unchanged into the urine; however, it has been suggested that glyphosate can undergo gut microbial metabolism in humans (Motojyuku *et al.*, 2008) and rodents (Brewster *et al.*, 1991).

4.1.2 Absorption

(a) Humans

Data on the absorption of glyphosate via intake of food and water in humans were not available to the Working Group. Inhalation of glyphosate is considered to be a minor route of exposure in humans, because glyphosate is usually formulated as an isopropylamine salt with a very low vapour pressure (Tomlin, 2000).

In the Farm Family Exposure Study, 60% of farmers had detectable levels of glyphosate in 24-hour composite urine samples taken on the day they had applied a glyphosate-based formulation (Acquavella *et al.*, 2004). Farmers who did not use rubber gloves had higher urinary concentrations of glyphosate than those who did use gloves [indicating that dermal absorption is a relevant route of exposure]. In a separate study, detectable levels of glyphosate were found in urine samples from farm families and non-farm families (Curwin *et al.*, 2007).

In accidental and deliberate intoxication cases involving ingestion of glyphosate-based formulations, glyphosate was readily detectable in the blood (Zouaoui *et al.*, 2013). After deliberate or accidental ingestion, one glyphosate-based formulation was found to be more lethal to humans than another (Sørensen & Gregersen, 1999). [Greater lethality was attributed to the presence of trimethylsulfonium counterion, which might facilitate greater absorption after oral exposure.]

Small amounts of glyphosate can be absorbed after dermal exposures in humans in vitro. For example, when an aqueous solution of 1% glyphosate was applied in an in-vitro human skin model, only 1.4% of the applied dose was absorbed through the skin. Glyphosate is typically formulated as an isopropylamine salt, and is dissolved in a water-based vehicle, while the stratum corneum is a lipid-rich tissue (Wester et al., 1991). In-vitro studies using human skin showed that percutaneous absorption of a glyphosate-based formulation was no more than 2% of the administered dose over a concentration range of 0.5–154 µg/cm^2 and a topical volume range of 0.014–0.14 mL/cm^2. In addition, very little glyphosate (≤ 0.05% of the administered dose) was sequestered in the stratum corneum after dermal application (Wester et al., 1991).

In the human Caco-2 cell line, an in-vitro model of intestinal enterocytes, glyphosate (> 10 mg/mL) was shown to significantly disrupt barrier properties, leading to an increase in paracellular permeability (transport of substances that pass through the intercellular space between the cells) (Vasiluk et al., 2005).

(b) Experimental systems

Three studies have been conducted to investigate the absorption of a single oral dose of glyphosate in rats (Brewster et al., 1991; Chan & Mahler, 1992; EPA, 1993b).

In male Sprague-Dawley rats given [^{14}C]-labelled glyphosate (10 mg/kg bw), the majority of the radiolabel was associated with the gastrointestinal contents and small intestinal tissue 2 hours after administration (Brewster et al., 1991). Approximately 35–40% of the administered dose was found to be absorbed from the gastrointestinal tract. Urinary and faecal routes of elimination were equally important. [The Working Group concluded that glyphosate is incompletely absorbed from the gastrointestinal tract after oral exposure in rats.]

In a study by the United States National Toxicology Programme (NTP) in Fisher 344 rats, 30% of the administered oral dose (5.6 mg/kg bw) was absorbed, as determined by urinary excretion data (Chan & Mahler, 1992). This finding was in accordance with the previously described study of oral exposure in rats (Brewster et al., 1991).

In a study reviewed by the EPA, Sprague-Dawley rats were given an oral dose of glyphosate (10 mg/kg bw); 30% and 36% of the administered dose was absorbed in males and females, respectively (EPA, 1993b). At a dose that was ~10-fold higher (1000 mg/kg bw), oral absorption of glyphosate by the rats was slightly reduced.

In a 14-day feeding study in Wistar rats given glyphosate at dietary concentrations of up to 100 ppm, only ~15% of the administered dose was found to be absorbed (JMPR, 2006). In New Zealand White rabbits or lactating goats given glyphosate as single oral doses (6–9 mg/kg bw), a large percentage of the administered dose was recovered in the faeces [suggesting very poor gastrointestinal absorption of glyphosate in these animal models] (JMPR, 2006).

In monkeys given glyphosate by dermal application, percutaneous absorption was estimated to be between 1% and 2% of the administered dose (Wester et al., 1991). Most of the administered dose was removed by surface washes of the exposed skin.

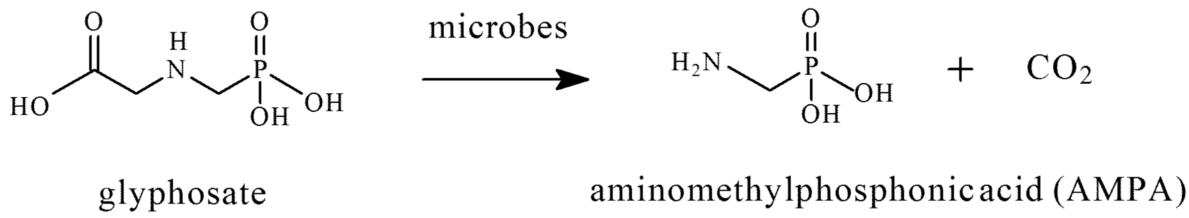
4.1.3 Distribution

(a) Humans

No data in humans on the distribution of glyphosate in systemic tissues other than blood were available to the Working Group. In cases of accidental or deliberate intoxication involving ingestion of glyphosate-based formulations, glyphosate was measured in blood. Mean blood concentrations of glyphosate were 61 mg/L and 4146 mg/L in mild-to-moderate cases of intoxication and in fatal cases, respectively (Zouaoui et al., 2013).

One report, using optical spectroscopy and molecular modelling, indicated that glyphosate could bind to human serum albumin, mainly by hydrogen bonding; however, the fraction of glyphosate that might bind to serum proteins in blood was not actually measured (Yue et al., 2008).

Fig. 4.1 Microbial metabolism of glyphosate to AMPA



Glyphosate is degraded to AMPA by microbial metabolism
Compiled by the Working Group

(b) Experimental systems

In Sprague-Dawley rats given a single oral dose of glyphosate (100 mg/kg bw), glyphosate concentrations in plasma reached peak levels, then declined slowly from day 1 to day 5 (Bernal *et al.*, 2010). The plasma data appeared to fit a one-compartment model with an elimination rate constant of k_{el} = 0.021 hour^{-1}. [The Working Group estimated the elimination half-life of glyphosate to be 33 hours.] Tissue levels of glyphosate were not determined in this study. In a study by Brewster *et al.* (1991), the tissue levels of glyphosate at 2, 6.3, 28, 96, and 168 hours in Sprague-Dawley rats given a single oral dose (10 mg/kg bw) declined rapidly. Tissues with the greatest amounts of detectable radiolabel (> 1% of the administered dose) were the small intestine, colon, kidney, and bone. Peak levels were reached in small intestine tissue and blood by 2 hours, while peak levels in other tissues occurred at 6.3 hours after dosing. After 7 days, the total body burden of [^{14}C]-labelled residues was ~1% of the administered dose, and was primarily associated with the bone (~1 ppm). In every tissue examined after administration of [^{14}C]-labelled glyphosate, essentially 100% of the radiolabel that was present in the tissue was unmetabolized parent glyphosate. Thus, essentially 100% of the body burden was parent compound, with no significant persistence of glyphosate after 7 days (Brewster *et al.*, 1991). In a 14-day feeding study in Wistar rats given diets containing glyphosate at 100 ppm, glyphosate reached steady-state levels in the blood by day 6 (JMPR, 2006). The tissue concentrations of glyphosate had the following rank order: kidneys > spleen > fat > liver. Tissue levels declined rapidly after cessation of exposure to glyphosate. A second study in rats given glyphosate (10 mg/kg bw per day, 14 days) followed by a single oral dose of [^{14}C]-glyphosate (at 10 mg/kg bw) showed that repeated dosing did not alter the tissue distribution of glyphosate (JMPR, 2006).

In rhesus monkeys, tissues harvested 7 days after dermal exposures to [^{14}C]-labelled glyphosate did not contain radiolabel at detectable levels (Wester *et al.*, 1991).

4.1.4 Metabolism and modulation of metabolic enzymes

(a) Metabolism

Glyphosate is degraded in the environment by soil microbes, primarily to AMPA and carbon dioxide (Fig. 4.1; Jacob *et al.*, 1988). A minor pathway for the degradation of glyphosate in bacteria (*Pseudomonas sp.* strain LBr) is via conversion to glycine (Jacob *et al.*, 1988). In a case of deliberate poisoning with a glyphosate-based formulation, small amounts of AMPA (15.1 µg/mL) were detectable in the blood (Motojyuku *et al.*, 2008) [suggesting that this pathway might also operate in humans]. In rats given a single high oral dose of glyphosate (100 mg/kg bw), small amounts of AMPA were detected in the plasma (Bernal *et al.*, 2010). In male Sprague-Dawley rats given an oral dose of glyphosate (10 mg/kg bw), a very small amount of AMPA (< 0.04% of the administered dose) was detected in the colon 2 hours after dosing; this was attributed to intestinal microbial metabolism (Brewster *et al.*, 1991).

(b) Modulation of metabolic enzymes

(i) Humans

In human hepatic cell lines, treatment with one of four glyphosate-based formulations produced by the same company was shown to enhance CYP3A4 and CYP1A2 levels, while glutathione transferase levels were reduced (Gasnier *et al.*, 2010). [The Working Group noted that it was not clear whether the effects were caused by glyphosate alone or by the adjuvants contained in the formulation.]

(ii) Experimental systems

Exposure of Wistar rats to a glyphosate-based formulation significantly altered some hepatic xenobiotic enzyme activities (Larsen *et al.*, 2014). Liver microsomes obtained from male and female rats treated with the formulation exhibited ~50% reductions in cytochrome P450 (CYP450) content compared with control (untreated) rats. However, opposing effects were observed when assessing 7-ethoxycoumarin *O*-deethylase activity (7-ECOD, a non-specific CYP450 substrate). Female rats treated with the glyphosate-based formulation exhibited a 57% increase in hepatic microsomal 7-ECOD activity compared with controls, while male rats treated with the formulation exhibited a 58% decrease in this activity (Larsen *et al.*, 2014). [The Working Group noted that it was not clear whether the effects were caused by glyphosate alone or by adjuvants contained in the formulation.]

4.1.5 Excretion

(a) Humans

Excretion of glyphosate in humans was documented in several biomonitoring studies. For example, as part of the Farm Family Exposure Study, urinary concentrations of glyphosate were evaluated immediately before, during, and after glyphosate application in 48 farmers and their spouses and children (Acquavella *et al.*, 2004). Dermal contact with glyphosate during mixing, loading, and application was considered to be the main route of exposure in the study. On the day the herbicide was applied, 60% of the farmers had detectable levels of glyphosate in 24-hour composite urine samples, as did 4% of their spouses and 12% of children. For farmers, the geometric mean concentration was 3 µg/L, the maximum value was 233 µg/L, and the highest estimated systemic dose was 0.004 mg/kg bw (Acquavella *et al.*, 2004). In a separate study, detectable levels of glyphosate were excreted in the urine of members of farm families and of non-farm families, with geometric means ranging from 1.2 to 2.7 µg/L (Curwin *et al.*, 2007).

In a study of a rural population living near areas sprayed for drug eradication in Colombia (see Section 1.4.1, Table 1.5), mean urinary glyphosate concentrations were 7.6 µg/L (range, undetectable to 130 µg/L) (Varona *et al.*, 2009). AMPA was detected in 4% of urine samples (arithmetic mean, 1.6 µg/L; range, undetectable to 56 µg/L).

(b) Experimental systems

In an NTP study in Fisher 344 rats given a single oral dose of [^{14}C]-labelled glyphosate (5.6 or 56 mg/kg bw), it was shown that > 90% of the radiolabel was eliminated in the urine and faeces within 72 hours (Chan & Mahler, 1992). In Sprague-Dawley rats given [^{14}C]-labelled glyphosate at an oral dose of 10 or 1000 mg/kg bw, ~60–70% of the administered dose was excreted in the faeces, and the remainder in the urine (EPA, 1993b). By either route, most (98%) of the administered dose was excreted as unchanged parent compound. AMPA was the only metabolite found in the urine (0.2–0.3% of the administered dose) and faeces (0.2–0.4% of the administered dose). [The large amount of glyphosate excreted in the faeces is consistent with its poor oral absorption.] Less than 0.3% of the administered dose was expired as carbon dioxide.

In rhesus monkeys given glyphosate as an intravenous dose (9 or 93 μg), > 95% of the administered dose was excreted in the urine (Wester *et al.*, 1991). Nearly all the administered dose was eliminated within 24 hours. In contrast, in rhesus monkeys given glyphosate by dermal application (5400 μg/20 cm ^{2}), only 2.2% of the administered dose was excreted in the urine within 7 days (Wester *et al.*, 1991).

Overall, systemically absorbed glyphosate is not metabolized efficiently, and is mainly excreted unchanged into the urine.

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

Glyphosate has been studied for genotoxic potential in a wide variety of assays. Studies carried out in exposed humans, in human cells in vitro, in other mammals in vivo and in vitro, and in non-mammalian systems in vivo and in vitro, respectively, are summarized in Table 4.1, Table 4.2, Table 4.3, Table 4.4, and Table 4.5. [A review article by Kier & Kirkland (2013) summarized the results of published articles and unpublished reports of studies pertaining to the genotoxicity of glyphosate and glyphosate formulations. A supplement to this report contained information on 66 unpublished regulatory studies. The conclusions and data tables for each individual study were included in the supplement; however, the primary study reports from which these data were extracted were not available to the Working Group. The information provided in the supplement was insufficient regarding topics such as details of statistical methods, choice of the highest dose tested, and verification of the target tissue exposure. The Working Group determined that the information in the supplement to Kier & Kirkland (2013) did not meet the criteria for data inclusion as laid out in the Preamble to the *IARC Monographs*, being neither "reports that have been published or accepted for publication in the openly available scientific literature" nor "data from governmental reports that are publicly available" (IARC, 2006). The review article and supplement were not considered further in the evaluation.]

(a) *Humans*

(i) *Studies in exposed humans*

See Table 4.1

In exposed individuals (n = 24) living in northern Ecuador in areas sprayed with a glyphosate-based formulation, a statistically significant increase in DNA damage (DNA strand breaks) was observed in blood cells collected 2 weeks to 2 months after spraying (Paz-y-Miño *et al.*, 2007). The same authors studied blood cells from individuals (n = 92) in 10 communities in Ecuador's northern border, who were sampled 2 years after the last aerial spraying with a herbicide mix containing glyphosate, and showed that their karyotypes were normal compared with those of a control group (Paz-y-Miño *et al.*, 2011).

Bolognesi *et al.* (2009) studied community residents (137 women of reproductive age and their 137 spouses) from five regions in Colombia. In three regions with exposures to glyphosate-based formulations from aerial spraying, blood samples were taken from the same individuals at three time-points (before spraying (baseline), 5 days after spraying and 4 months after spraying) to determine the frequency of micronucleus formation in lymphocytes. The baseline frequency of binucleated cells with micronuclei was significantly higher in subjects from the three regions where there had been aerial spraying with glyphosate-formulations and in a fourth region with pesticide exposure (but not through aerial spraying), compared with a reference region (without use of pesticide). The frequency of micronucleus formation in peripheral blood lymphocytes was significantly increased, compared with baseline levels in the same individuals, after aerial spraying with glyphosate-based formulations in each of the three regions (see Table 4.1 ; Bolognesi *et al.*, 2009). Immediately after spraying, subjects who reported direct contact with the glyphosate-based spray showed a higher frequency of binucleated cells with micronuclei. However, the increase in frequency of micronucleus formation observed immediately after spraying was not consistent with the rates of application used in the regions, and there was no association between self-reported direct contact with pesticide sprays and frequency of binucleated cells with micronuclei. In subjects from one but not other regions, the frequency of binucleated cells with micronuclei was significantly decreased 4 months after spraying, compared with immediately after spraying.

(ii) Human cells in vitro

See Table 4.2

Glyphosate induced DNA strand breaks (as measured by the comet assay) in liver Hep-2 cells (Mañas *et al.*, 2009a), lymphocytes (Mladinic *et al.*, 2009b; Alvarez-Moya *et al.*, 2014), GM38 fibroblasts, the HT1080 fibrosarcoma cell line (Monroy *et al.*, 2005), and the TR146 buccal carcinoma line (Koller *et al.*, 2012). DNA strand breaks were induced by AMPA in Hep-2 cells (Mañas *et al.*, 2009b), and by a glyphosate-based formulation in the TR146 buccal carcinoma cell line (Koller *et al.*, 2012).

In human lymphocytes, AMPA (Mañas *et al.*, 2009b), but not glyphosate (Mañas *et al.*, 2009a), produced chromosomal aberrations. Glyphosate did not induce a concentration-related increase in micronucleus formation in human lymphocytes at levels estimated to correspond to occupational and residential exposure (Mladinic *et al.*, 2009a). Sister-chromatid exchange was induced by glyphosate (Bolognesi *et al.*, 1997), and by a glyphosate-based formulation (Vigfusson & Vyse, 1980; Bolognesi *et al.*, 1997) in human lymphocytes exposed in vitro.

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.3

The ability of glyphosate or a glyphosate-based formulation to induce DNA adducts was studied in mice given a single intraperitoneal dose. Glyphosate induced DNA adducts (8-hydroxy deoxyguanosine) in the liver, but not in the kidney, while a glyphosate-based formulation caused a slight increase in DNA adducts in the kidney, but not in the liver (Bolognesi *et al.*, 1997). Peluso *et al.* (1998) showed that a glyphosate-based formulation (glyphosate, 30.4%), but not glyphosate alone, caused DNA adducts (as detected by ^{32}P-DNA post-labelling) in mouse liver and kidney. Glyphosate and a glyphosate-based formulation produced DNA strand breaks in the liver and kidney after a single intraperitoneal dose (Bolognesi *et al.*, 1997).

In mice given a single dose of glyphosate by gavage, no genotoxic effect was observed by the dominant lethal test (EPA, 1980a).

After a single intraperitoneal dose, no chromosomal aberrations were observed in the bone marrow of rats treated with glyphosate (Li & Long 1988), while chromosomal aberrations were increased in the bone marrow of mice given a glyphosate-based formulation (glyphosate isopropylamine salt, ~41%) (Prasad *et al.*, 2009). A single oral dose of a glyphosate-based formulation did not cause chromosomal aberrations in mice (Dimitrov *et al.*, 2006).

In mice treated by intraperitoneal injection, a single dose of glyphosate did not cause

Table 4.1 Genetic and related effects of glyphosate in exposed humans

Tissue	Cell type (if specified)	End-point	Test	Description of exposure and controls	Response[a]/ significance	Comments	Reference
Blood	NR	DNA damage	DNA strand breaks, comet assay	24 exposed individuals in northern Ecuador; areas sprayed with glyphosate-based formulation (sampling 2 weeks to 2 months after spraying); control group was 21 non-exposed individuals	+ $P < 0.001$		Paz-y-Miño et al. (2007)
Blood	NR	Chromosomal damage	Chromosomal aberrations	92 individuals in 10 communities, northern border of Ecuador; sampling 2 years after last aerial spraying with herbicide mix containing glyphosate); control group was 90 healthy individuals from several provinces without background of smoking or exposure to genotoxic substances (hydrocarbons, X-rays, or pesticides)	–	182 karyotypes were considered normal [Smoking status, NR]	Paz-y-Miño et al. (2011)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	55 community residents, Nariño, Colombia; area with aerial glyphosate-based formulation spraying for coca and poppy eradication (glyphosate was tank-mixed with an adjuvant)	+ [$P < 0.001$]	P values for after spraying vs before spraying in the same individuals	Bolognesi et al. (2009)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	53 community residents, Putumayo, Colombia; area with aerial glyphosate-based formulation spraying for coca and poppy eradication (glyphosate was tank-mixed with an adjuvant)	+ [$P = 0.01$]	P values for after spraying vs before spraying in the same individuals	Bolognesi et al. (2009)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	27 community residents, Valle del Cauca, Colombia; area where glyphosate-based formulation was applied through aerial spraying for sugar-cane maturation (glyphosate was applied without adjuvant)	+ [$P < 0.001$]	P values for after spraying vs before spraying in the same individuals	Bolognesi et al. (2009)

[a] +, positive; –, negative
NR, not reported; vs, versus

micronucleus formation in the bone marrow (Rank *et al.*, 1993), although two daily doses did (Bolognesi *et al.*, 1997; Mañas *et al.*, 2009a). AMPA, the main metabolite of glyphosate, also produced micronucleus formation after two daily intraperitoneal doses (Mañas *et al.*, 2009b). Conflictingresults for micronucleus induction were obtained in mice exposed intraperitoneally to a glyphosate-based formulation. A single dose of the formulation at up to 200 mg/kg bw did not induce micronucleus formation in the bone marrow in one study (Rank *et al.* 1993), while it did increase micronucleus formation at 25 mg/kg bw in another study (Prasad *et al.*, 2009). Aftertwo daily intraperitoneal doses, a glyphosate-based formulation did not induce micronucleus formation at up to 200 mg/kg bw according to Grisolia (2002), while Bolognesi *et al.* (1997) showed that the formulation did induce micronucleus formation at 450 mg/kg bw. In mice given a single oral dose of a glyphosate-based formulation at 1080 mg/kg bw, no induction of micronuclei was observed (Dimitrov *et al.*, 2006).

(ii) Non-human mammalian cells in vitro

See Table 4.4

Glyphosate did not induce unscheduled DNA synthesis in rat primary hepatocytes, or *Hprt* mutation (with or without metabolic activation) in Chinese hamster ovary cells (Li & Long, 1988).

In bovine lymphocytes, chromosomal aberrations were induced by glyphosate in one study (Lioi *et al.*, 1998), but not by a glyphosate formulation in another study (Siviková & Dianovský, 2006). Roustan *et al.* (2014) demonstrated, in the CHO-K1 ovary cell line, that glyphosate induced micronucleus formation only in the presence of metabolic activation, while AMPA induced micronucleus formation both with and without metabolic activation. Sister-chromatid exchange was observed in bovine lymphocytes exposed to glyphosate (Lioi *et al.*, 1998) or a glyphosate formulation (in the absence but not the presence of metabolic activation) (Siviková & Dianovský, 2006).

(iii) Non-mammalian systems in vivo

See Table 4.5

Fish and other species

In fish, glyphosate produced DNA strand breaks in the comet assay in sábalo (Moreno *et al.*, 2014), European eel (Guilherme *et al.*, 2012b), zebrafish (Lopes *et al.*, 2014), and Nile tilapia (Alvarez-Moya *et al.*, 2014). AMPA also induced DNA strand breaks in the comet assay in European eel (Guilherme *et al.*, 2014b). A glyphosate-based formulation produced DNA strand breaks in numerous fish species, such as European eel (Guilherme *et al.*, 2010, 2012b, 2014a; Marques *et al.*, 2014, 2015), sábalo (Cavalcante *et al.*, 2008; Moreno *et al.*, 2014), guppy (De Souza Filho *et al.*, 2013), bloch (Nwani *et al.*, 2013), neotropical fish *Corydoras paleatus* (de Castilhos Ghisi & Cestari, 2013), carp (Gholami-Seyedkolaei *et al.*, 2013), and goldfish (Cavaş & Könen, 2007).

AMPA, the main metabolite of glyphosate, induced erythrocytic nuclear abnormalities (kidney-shaped and lobed nuclei, binucleate or segmented nuclei and micronuclei) in European eel (Guilherme *et al.*, 2014b). Micronucleus formation was induced by different glyphosate-based formulations in various fish(Grisolia, 2002; Cavaş & Könen, 2007; De Souza Filho *et al.*, 2013; Vera-Candioti *et al.*, 2013).

Glyphosate-based formulations induced DNA strand breaks in other species, including caiman (Poletta *et al.*, 2009), frog (Meza-Joya *et al.*, 2013), tadpoles (Clements *et al.*, 1997), and snail (Mohamed, 2011), but not in oyster (Akcha *et al.*, 2012), clam (dos Santos & Martinez, 2014), and mussel glochidia (Conners & Black, 2004). In earthworms, one glyphosate-based formulation induced DNA strand breaks while two others did not (Piola *et al.*, 2013; Muangphra *et al.*, 2014), highlighting the potential importance of components other than the active ingredient in the formulation.

Table 4.2 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in human cells in vitro

Tissue, cell line	End-point	Test	Results[a] Without metabolic activation	Results[a] With metabolic activation	Dose (LED or HID)	Comments	Reference
Glyphosate							
Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	3 mM [507.2 μg/mL]	$P < 0.01$; dose–response relationship ($r \geq 0.90$; $P < 0.05$)	Mañas et al. (2009a)
Lymphocytes	DNA damage	DNA strand breaks, standard and hOGG1 modified comet assay	+	+	3.5 μg/mL	With the hOGG1 modified comet assay, + S9, the increase was significant ($P < 0.01$) only at the highest dose tested (580 μg/mL)	Mladinic et al. (2009b)
Lymphocytes	DNA damage	DNA strand breaks, comet assay	+	NT	0.0007 mM [0.12 μg/mL]	$P \leq 0.01$	Alvarez-Moya et al. (2014)
Fibroblast GM 38	DNA damage	DNA strand breaks, comet assay	+	NT	4 mM [676 μg/mL]	$P < 0.001$	Monroy et al. (2005)
Fibroblast GM 5757	DNA damage	DNA strand breaks, comet assay	(+)	NT	75 mM [12 680 μg/mL]	Glyphosate (ineffective alone, data NR) increased strand breaks induced by H_2O_2 (40 or 50 μM) ($P < 0.004$ vs H_2O_2 alone)	Lueken et al. (2004)
Fibrosarcoma HT1080	DNA damage	DNA strand breaks, comet assay	+	NT	4.75 mM [803 μg/mL]	$P < 0.001$	Monroy et al. (2005)
Buccal carcinoma TR146	DNA damage	DNA strand breaks, SCGE assay	+	NT	20 μg/mL	Dose-dependent increase ($P \leq 0.05$)	Koller et al. (2012)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	NT	6 mM [1015 μg/mL]		Mañas et al. (2009a)
Lymphocytes	Chromosomal damage	Micronucleus formation	–	(+)	580 μg/mL	$P < 0.01$ at the highest exposure + S9 No concentration-related increase in micronuclei containing the centromere signal (C+)	Mladinic et al. (2009a)

Table 4.2 (continued)

Tissue, cell line	End-point	Test	Results[a]		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	1000 µg/mL	$P < 0.05$	Bolognesi *et al.* (1997)
AMPA							
Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	4.5 mM [500 µg/mL]	$P < 0.05$ at 4.5 mM; $P < 0.01$ at up to 7.5 mM Dose–response relationship (r ≥ 0.90; $P < 0.05$)	Mañas *et al.* (2009b)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	+	NT	1.8 mM [200 µg/mL]	$P < 0.05$	Mañas *et al.* (2009b)
Glyphosate-based formulations							
Liver HepG2	DNA damage	DNA strand breaks, comet assay	(+)	NT	5 ppm	Glyphosate, 400 g/L Dose-dependent increase; greatest increase at 10 ppm Statistical analysis, NR	Gasnier *et al.* (2009)
Buccal carcinoma TR146	DNA damage	DNA strand breaks, SCGE assay	+	NT	20 µg/mL	Glyphosate acid, 450g/L Dose-dependent increase ($P \leq 0.05$)	Koller *et al.* (2012)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	250 µg/mL	$P < 0.001$ No growth at 25 mg/mL	Vigfusson & Vyse (1980)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	100 µg/mL	Glyphosate, 30.4% $P < 0.05$	Bolognesi *et al.* (1997)

[a] +, positive; -, negative; (+) or (-) positive/negative in a study with limited quality

AMPA, aminomethyl phosphonic acid; HID, highest ineffective dose; hOGG1, human 8-hydroxyguanosine DNA-glycosylase; LED, lowest effective dose; NR, not reported; NT, not tested; S9, 9000 × *g* supernatant; SCGE, single cell gel electrophoresis; vs, versus

Micronucleus formation was induced by a glyphosate-based formulation (glyphosate, 36%) in earthworms (Muangphra *et al.*, 2014), and by a different glyphosate-based formulation in caiman (Poletta *et al.*, 2009, 2011), and frog (Yadav *et al.*, 2013).

Insects

In standard *Drosophila melanogaster*, glyphosate induced mutation in the test for somatic mutation and recombination, but not in a cross of flies characterized by an increased capacity for CYP450-dependent bioactivation (Kaya *et al.*, 2000). A glyphosate-based formulation also caused sex-linked recessive lethal mutations in *Drosophila* (Kale *et al.*, 1995).

Plants

In plants, glyphosate produced DNA damage in *Tradescantia* in the comet assay (Alvarez-Moya *et al.*, 2011). Chromosomal aberration was induced after exposure to glyphosate in fenugreek (Siddiqui *et al.*, 2012), and in onion in one study (Frescura *et al.*, 2013), but not in another (Rank *et al.*, 1993). A glyphosate-based formulation also induced chromosomal aberration in barley roots (Truta *et al.*, 2011) and onion (Rank *et al.*, 1993), but not in *Crepis capillaris* (hawksbeard) (Dimitrov *et al.*, 2006). Micronucleus formation was not induced by glyphosate in *Vicia faba* bean (De Marco *et al.*, 1992) or by a glyphosate-based formulation in *Crepis capillaris* (Dimitrov *et al.*, 2006).

(iv) Non-mammalian systems in vitro

See Table 4.6

Glyphosate induced DNA strand breaks in erythrocytes of tilapia fish, as demonstrated by comet assay (Alvarez-Moya *et al.*, 2014).

Glyphosate did not induce mutation in *Bacillus subtillis*, *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, or in *Escherichia coli* WP2, with or without metabolic activation (Li & Long, 1988). However, Rank *et al.* (1993) demonstrated that a glyphosate-based formulation was mutagenic in *S. typhimurium* TA98 in the absence of metabolic activation, and in *S. typhimurium* TA100 in the presence of metabolic activation.

4.2.2 Receptor-mediated mechanisms

(a) Sex-hormone pathway disruption

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

In hormone-dependent T47D breast cancer cells, the proliferative effects of glyphosate (10^{-6} to 1 μM) (see Section 4.2.4) and those of 17β-estradiol (the positive control) were mitigated by the estrogen receptor antagonist, ICI 182780; the proliferative effect of glyphosate was completely abrogated by the antagonist at a concentration of 10 nM (Thongprakaisang *et al.*, 2013). Glyphosate also induced activation of the estrogen response element (ERE) in T47D breast cancer cells that were stably transfected with a triplet ERE-promoter-luciferase reporter gene construct. Incubation with ICI 182780 at 10 nM eliminated the response. When the transfected cells were incubated with both 17β-estradiol and glyphosate, the effect of 17β-estradiol was reduced and glyphosate behaved as an estrogen antagonist. After 6 hours of incubation, glyphosate increased levels of estrogen receptors ERα and ERβ in a dose-dependent manner in T47D cells; after 24 hours, only ERβ levels were increased and only at the highest dose of glyphosate. [These findings suggested that the proliferative effects of glyphosate on T47D cells are mediated by ER.]

In human hepatocarcinoma HepG2 cells, four glyphosate-based formulations produced by the same company had a marked effect on the activity and transcription of aromatase, while glyphosate alone differed from controls, but not significantly so (Gasnier *et al.*, 2009).

Table 4.3 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-human mammals in vivo

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Glyphosate								
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA adducts, 8-OHdG by LC/UV	+	300 mg/kg bw	i.p.; 1×; sampled after 8 and 24 h	Single dose tested only $P < 0.05$ after 24 h	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA adducts, 8-OHdG by LC/UV	–	300 mg/kg bw	i.p.; 1×; sampled after 8 and 24 h	Single dose tested only	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M, F)	Kidney	DNA damage	DNA adducts, ^{32}P-DNA post labelling	–	270 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt	Peluso *et al.* (1998)
Mouse, Swiss CD1 (M, F)	Liver	DNA damage	DNA adducts, ^{32}P-DNA post labelling	–	270 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt	Peluso *et al.* (1998)
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA strand breaks, alkaline elution assay	+	300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Single dose tested only $P < 0.05$ after 4 h	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA strand breaks, alkaline elution assay	+	300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Single dose tested only $P < 0.05$ after 4 h	Bolognesi *et al.* (1997)
Mouse, CD-1 (M)	Uterus after mating	Mutation	Dominant lethal test	–	2000 mg/kg bw	Oral gavage; 1 ×	Proportion of early resorptions evaluated after mating of non-treated females with glyphosate-treated male mice	EPA (1980)
Rat, Sprague-Dawley (M, F)	Bone marrow	Chromosomal damage	Chromosomal aberrations	–	1000 mg/kg bw	i.p.; 1 ×; sampled after 6, 12 and 24 h	Single dose tested only	Li & Long (1988)
Mouse, NMRI-bom (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 1 ×; sampled after 24 and 48 h	Glyphosate isopropylamine salt	Rank *et al.* (1993)
Mouse, Swiss CD1 (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	300 mg/kg bw	i.p.; 2 × 150 mg/kg bw with 24 h interval; sampled 6 or 24 h after the last injection	Single dose tested only $P < 0.05$ after 24 h	Bolognesi *et al.* (1997)

Table 4.3 (continued)

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, Balb C (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	400 mg/kg bw	i.p.; one injection per 24 h, 2 × 200, sampled 24 h after the last injection	*P* < 0.01 at the highest dose (400 mg/kg bw)	Mañas *et al.* (2009a)
AMPA								
Mouse, Balb C (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	200 mg/kg bw	i.p.; one injection per 24 h, 2 × 100, sampled 24 h after the last injection	*P* < 0.01 at the lowest dose (200 mg/kg bw)	Mañas *et al.* (2009b)
Glyphosate-based formulations								
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA adducts, 8-OHdG by LC/UV	–	~300 mg/kg bw	i.p.; 1 ×, sampled after 8 and 24 h	Glyphosate, 30.4% Single dose tested only	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA adducts, 8-OHdG by LC/UV	+	~300 mg/kg bw	i.p.; 1 ×, sampled after 8 and 24 h	Glyphosate, 30.4% Single dose tested only *P* < 0.05	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M, F)	Kidney	DNA damage	DNA adducts, ^{32}P-DNA post labelling	+	400 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 30.4%	Peluso *et al.* (1998)
Mouse, Swiss CD1 (M, F)	Liver	DNA damage	DNA adducts, ^{32}P-DNA post labelling	+	400 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 30.4%	Peluso *et al.* (1998)
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA strand breaks, alkaline elution assay	+	~300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Glyphosate, 30.4% Single dose tested only *P* < 0.05 only after 4 h	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA strand breaks, alkaline elution assay	+	~300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Glyphosate, 30.4% Single dose tested only *P* < 0.05 only after 4 h	Bolognesi *et al.* (1997)
Mouse, C57BL (M)	Bone marrow (PCE)	Chromosomal damage	Chromosomal aberrations	–	1080 mg/kg bw	p.o. in distilled water; 1 ×; sampled after 6, 24, 48, 72, 96 and 120 h	Single dose tested only	Dimitrov *et al.* (2006)

Table 4.3 (continued)

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, Swiss albino (M)	Bone marrow	Chromosomal damage	Chromosomal aberrations	+	25 mg/kg bw	i.p.; 1 ×; sampled after 24, 48 and 72 h	Glyphosate isopropylamine salt, > 41% The percentage of aberrant cells was increased vs control in a dose- and time-dependent manner ($P < 0.05$)	Prasad et al. (2009)
Mouse, NMRI-bom (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 480 g/L The percentage of PCE decreased	Rank et al. (1993)
Mouse, Swiss (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 2 × within 24 h interval and sampled 24 h after the last injection	Glyphosate isopropylammonium salt, 480 g/L	Grisolia (2002)
Mouse, Swiss albino (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	25 mg/kg bw	i.p.; 1 × ; sampled after 24, 48 and 72 h	Glyphosate isopropylamine salt, > 41% Significant induction of micronuclei vs control at both doses and all times ($P < 0.05$)	Prasad et al. (2009)
Mouse, Swiss CD1 (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	450 mg/kg bw	i.p.; 2 × 225 mg/kg with 24 h interval; sampled 6 or 24 h after the last injection	Glyphosate, 30.4% Single dose tested only $P < 0.05$ after 6 h and 24 h	Bolognesi et al. (1997)
Mouse, C57BL (M)	Bone marrow	Chromosomal damage	Micronucleus formation	–	1080 mg/kg bw	p.o. in distilled water; 1 × ; sampled after 24, 48, 72, 96 and 120 h	Single dose tested only	Dimitrov et al. (2006)

[a] +, positive; -, negative; (+) or (-) positive/negative in a study with limited quality
bw, body weight; F, female; h, hour; HID, highest effective dose; i.p., intraperitoneal; LC, liquid chromatography; LED, lowest effective dose; M, male; PCE, polychromatic erythrocytes; p.o., oral; 8-OHdG, 8-hydroxydeoxyguanosine; UV, ultraviolet

Table 4.4 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-human mammalian cells in vitro

Species	Tissue, cell line	End-point	Test	Results[a]		Dose (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Glyphosate								
Rat, Fisher F334	Hepatocytes	DNA damage	Unscheduled DNA synthesis	–	NT	125 μg/mL		Li & Long (1988)
Hamster, Chinese	CHO-K_1BH_4 ovary, cell line	Mutation	*Hprt* mutation	–	–	22 500 μg/mL		Li & Long (1988)
Bovine	Lymphocytes	Chromosomal damage	Chromosomal aberrations	+	NT	17 μM [3 μg/mL]	$P < 0.05$	Lioi et al. (1998)
Hamster, Chinese	CHO-K1 ovary cell line	Chromosomal damage	Micronucleus formation	–	+	10 μg/mL	$P \leq 0.001$, in the dark +S9 Negative –S9 in the dark or with light irradiation	Roustan et al. (2014)
Bovine	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	17 μM [3 μg/mL]	$P < 0.05$	Lioi et al. (1998)
AMPA								
Hamster, Chinese	CHO-K1 ovary cell line	Chromosomal damage	Micronucleus formation	+	+	0.01 μg/mL	$P \leq 0.05$, in the dark –S9 Highest increase was observed at very low dose (0.0005 μg/mL) –S9 but with light-irradiation ($P < 0.01$)	Roustan et al. (2014)
Glyphosate-based formulations								
Bovine	Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	NT	1120 μM [190 μg/mL]	Glyphosate, 62%	Šivikova & Dianovský (2006)
Bovine	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	–	56 μM [9.5 μg/mL]	Glyphosate, 62% Time of exposure, 24 h $P < 0.01$, –S9, at ≥ 56 μM	Šivikova & Dianovský (2006)

[a] +, positive; –, negative; (+), weakly positive

AMPA, aminomethyl phosphonic acid; HIC, highest ineffective concentration; *Hprt*, hypoxanthine guanine phosphoribosyl transferase gene; LEC, lowest effective concentration; NT, not tested

Table 4.5 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-mammalian systems in vivo

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Glyphosate							
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and gill cells	DNA damage	DNA strand breaks, comet assay	+	0.48 mg/L	Time of exposure 6, 24, and 96 h For erythrocytes, $P = 0.01$ after 6 h, and $P = 0.014$ after 96 h; no significant increase after 24 h For gill cells, $P = 0.02$ only after 6 h at 2.4 mg/L	Moreno *et al.* (2014)
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay	+	0.0179 mg/L	Time of exposure 1 and 3 days $P < 0.05$	Guilherme *et al.* (2012b)
Fish	*Danio rerio* (zebrafish) sperm	DNA damage	DNA strand breaks, acridine orange method	+	10 mg/L	After 96 h, DNA integrity was 78.3 ± 3.5%, significantly reduced from control (94.7 ± 0.9%) and 5 mg/L (92.6 ± 1.9%), ($P < 0.05$)	Lopes *et al.* (2014)
Fish	*Oreochromis niloticus* (Nile tilapia) branchial erythrocytes	DNA damage	DNA strand breaks, comet assay	+	7 µM [1.2 mg/L]	Time of exposure, 10 days $P < 0.001$ with concentrations ≥ 7 µM	Alvarez-Moya *et al.* (2014)
Oyster	Oyster spermatozoa	DNA damage	DNA strand breaks, comet assay	–	0.005 mg/L	Time of exposure, 1 h	Akcha *et al.* (2012)
Insect	*Drosophila* standard cross	Mutation	SMART	+	1 mM [0.169 mg/L]	Purity, 96% Increased frequency of small single spots (≥ 1 mM) and total spots (≥ 2 mM) $P = 0.05$	Kaya *et al.* (2000)
Insect	*Drosophila melanogaster*, high bioactivation cross	Mutation	SMART	–	10 mM [1.69 mg/L]	Purity, 96%	Kaya *et al.* (2000)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Plant systems	*Tradescantia* clone 4430 (spiderworts), staminal hair nuclei	DNA damage	DNA strand breaks, comet assay	+	0.0007 mM [0.12 μg/mL]	Glyphosate isopropylamine salt *P* < 0.01 for directly exposed nuclei (dose-dependent increase) and plants	Alvarez-Moya *et al.* (2011)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	+	3%	Single dose tested only Partial but significant reversal with distilled water	Frescura *et al.* (2013)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	–	2.88 μg/mL	Glyphosate isopropylamine	Rank *et al.* (1993)
Plant systems	*Trigonella foenum-graecum* L. (fenugreek)	Chromosomal damage	Chromosomal aberrations	+	0.2%	*P* < 0.001; positive dose–response relationship	Siddiqui *et al.* (2012)
Plant systems	*Vicia faba* (bean)	Chromosomal damage	Micronucleus formation	–	1400 ppm (1400 μg/g of soil)	Tested with two types of soil, but not without soil	De Marco *et al.* (1992)
AMPA							
Fish	*Anguilla anguilla* L. (European eel)	DNA damage	DNA strand breaks, comet assay	+	0.0118 mg/L	Time of exposure, 1 and 3 days *P* < 0.05 after 1 day of exposure	Guilherme *et al.* (2014b)
Fish	*Anguilla anguilla* L. (European eel)	Chromosomal damage	Other (ENA)	+	0.0236 mg/L	*P* < 0.05 only at highest dose after 3 day exposure (not after 1 day)	Guilherme *et al.* (2014b)
Glyphosate-based formulations							
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay	+	0.058 mg/L	*P* < 0.05 Positive dose–response relationship	Guilherme *et al.* (2010)
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.058 mg/L	Glyphosate-based formulation, 30.8% Time of exposure, 1 and 3 days With FPG, *P* < 0.05; with comet assay alone, *P* < 0.05 at 116 μg/L	Guilherme *et al.* (2012b)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.116 mg/L	Single dose tested only Time of exposure, 3 days; recovery from non-specific DNA damage, but not oxidative DNA damage, 14 days after exposure $P < 0.05$	Guilherme *et al.* (2014a)
Fish	*Anguilla anguilla* L. (European eel), liver	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.058 mg/L	Glyphosate-based formulation, 485 g/L Time of exposure, 3 days $P < 0.05$	Marques *et al.* (2014, 2015)
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and bronchial cells	DNA damage	DNA strand breaks, comet assay	+	10 mg/L	Single dose tested only, for 6, 24, and 96 h $P < 0.05$ for both erythrocytes and bronchial cells	Cavalcante *et al.* (2008)
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and gill cells	DNA damage	DNA strand breaks, comet assay	+	1 mg/L	Glyphosate-based formulation, 480 g/L Time of exposure, 6, 24 and 96 h $P < 0.001$ after 24 and 96 h in erythrocytes and 24 h in gill cells	Moreno *et al.* (2014)
Fish	*Poecilia reticulata* (guppy) gill erythrocytes	DNA damage	DNA strand breaks, comet assay	+	2.83 µL/L [1.833 mg/L]	Glyphosate, 64.8%, m/v (648 g/L) $P < 0.05$	De Souza Filho *et al.* (2013)
Fish	*Channa punctatus* (bloch), blood and gill cells	DNA damage	DNA strand breaks, comet assay	+	3.25 mg/L	Exposure continued for 35 days; blood and gill cells collected on day 1, 7, 14, 21, 28 and 35 $P < 0.01$, for blood and gill cells; DNA damage increased with time and concentration	Nwani *et al.* (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Corydoras paleatus* (blue leopard corydoras, mottled corydoras and peppered catfish), blood and hepatic cells	DNA damage	DNA strand breaks, comet assay	+	0.0067 mg/L	Glyphosate, 48% (corresponding to 3.20 µg/L) Single dose tested only, for 3, 6, and 9 days $P < 0.01$, in blood and in liver cells	de Castilhos Ghisi & Cestari (2013)
Fish	*Cyprinus carpio* Linnaeus (carp), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	2 mg/L (10% LC_{50}, 96 h)	Glyphosate, equivalent to 360 g/L Single dose tested only, for 16 days $P < 0.01$	Gholami-Seyedkolaei *et al.* (2013)
Fish	*Carassius auratus* (goldfish), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	5 ppm	Glyphosate equivalent to 360 g/L Time of exposure, 2, 4 and 6 days After 48 h: $P < 0.05$ (5 mg/L) and $P < 0.001$ (10 and 15 mg/L)	Cavas & Könen (2007)
Fish	*Prochilodus lineatus* (sábalo) erythrocytes	Chromosomal damage	Micronucleus formation	–	10 mg/L	Single dose tested only, for 6, 24, and 96 h Nuclear abnormalities (lobed nuclei, segmented nuclei and kidney-shaped nuclei)	Cavalcante *et al.* (2008)
Fish	*Corydoras paleatus* (blue leopard corydoras, mottled corydoras and peppered catfish), blood and hepatic cells	Chromosomal damage	Micronucleus formation	–	0.0067 mg/L	Glyphosate, 48% (corresponding to 3.20 µg/L) Single dose tested only, for 3, 6 and 9 days	de Castilhos Ghisi & Cestari (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Tilapia rendalli* (redbreast tilapia) blood erythrocytes	Chromosomal damage	Micronucleus formation	+	42 mg/kg bw	Glyphosate, 480 g/L Increased frequency of micronucleus formation vs control ($P < 0.05$) in blood samples collected 4 days after a single intra-abdominal injection of 42, 85, or 170 mg/kg bw	Grisolia (2002)
Fish	*Carassius auratus* (goldfish), erythrocytes	Chromosomal damage	Micronucleus formation	+	5 ppm	Glyphosate equivalent to 360 g/L Time of exposure, 2, 4 and 6 days Statistically significant differences: 96 h ($P < 0.05$); 144 h ($P < 0.01$)	Cavas & Könen (2007)
Fish	*Poecilia reticulata* (guppy) gill erythrocytes	Chromosomal damage	Micronucleus formation, ENA	+	1.41 µL/L [0.914 mg/L]	Glyphosate, 64.8%, m/v (648 g/L) Micronucleus formation, $P < 0.01$ Other nuclear abnormalities, $P < 0.05$ at 1.41 to 5.65 µL/L; concentration-dependent ($r^2 = 0.99$)	De Souza Filho *et al.* (2013)
Fish	*Cnesterodon decemmaculatus* (Jenyns, 1842) peripheral blood erythrocytes	Chromosomal damage	Micronucleus formation	+	3.9 mg/L	Glyphosate, 48% Time of exposure, 48 and 96 h $P < 0.05$, with 3.9 and 7.8 mg/L for 48 and 96 h	Vera-Candioti *et al.* (2013)
Fish	*Cnesterodon decemmaculatus* (Jenyns, 1842) peripheral blood erythrocytes	Chromosomal damage	Micronucleus formation	+	22.9 mg/L	Glyphosate, 48% Time of exposure, 48 and 96 h $P < 0.01$, with 22.9 and 45.9 mg/L, and $P < 0.05$ at 68.8 mg/L, for 96 h	Vera-Candioti *et al.* (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Prochilodus lineatus* (sábalo) erythrocytes	Chromosomal damage	Chromosomal aberrations	–	10 mg/L	Single dose tested only, for 6, 24, and 96 h Nuclear abnormalities (lobed nuclei, segmented nuclei and kidney-shaped nuclei)	Cavalcante *et al.* (2008)
Fish	*Anguilla anguilla* L. (European eel), peripheral mature erythrocytes	Chromosomal damage	Other (ENA)	+	0.058 mg/L	Time of exposure, 1 and 3 days Chromosomal breakage and/or chromosomal segregational abnormalities after 3 days of exposure, $P < 0.05$	Guilherme *et al.* (2010)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	0.500 mg/egg	Glyphosate, 66.2% In-ovo exposure; blood sampling at the time of hatching $P < 0.05$ in both experiments (50–1000 µg/egg in experiment 1; 500–1750 µg/egg in experiment 2)	Poletta *et al.* (2009)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	DNA damage	DNA strand breaks, comet assay	–	19 800 mg/L	Glyphosate, 66.2% Single dose tested only; in-ovo exposure First spraying exposure at the beginning of incubation period, a second exposure on day 35, then incubation until hatching	Poletta *et al.* (2011)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	Chromosomal damage	Micronucleus fomation	+	0.500 mg/egg	Glyphosate, 66.2% In-ovo exposure; blood sampling at the time of hatching $P < 0.05$ in both experiments (50–1000 µg/egg in experiment 1; 500–1750 µg/egg in experiment 2)	Poletta *et al.* (2009)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	Chromosomal damage	Micronucleus formation	+	19.8 g/L	Glyphosate, 66.2% One dose tested; in-ovo exposure First spraying exposure at the beginning of incubation period, a second exposure on day 35, then incubation until hatching. Micronucleus formation, $P < 0.001$ Damage index, $P < 0.001$	Poletta *et al.* (2011)
Frog tadpole	*Rana catesbeiana* (ouaouaron), blood	DNA damage	DNA strand breaks, comet assay	+	1.687 mg/L, p.o.	Time of exposure, 24 h $P < 0.05$, with 6.75 mg/L; and $P < 0.001$ with 27 mg/L (with 108 mg/L, all died within 24 h)	Clements *et al.* (1997)
Frog	*Eleutherodactylus johnstonei* (Antilles coqui), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	0.5 µg a.e./cm²	Glyphosate-based formulation, 480 g/L Exposure to an homogenate mist in a 300 cm² glass terrarium Time of exposure: 0.5, 1, 2, 4, 8 and 24 h $P < 0.05$	Meza-Joya *et al.* (2013)
Frog	*Euflictis cyanophlyctis* (Indian skittering frog), erythrocytes	Chromosomal damage	Micronucleus formation	+	1 mg a.e./L	Glyphosate isopropylamine salt, 41% Time of exposure: 24, 48, 72, and 96 h $P < 0.001$ at 24, 48, 72 and 96 h	Yadav *et al.* (2013)
Snail	*Biomphalaria alexandrina*, haemolymph	DNA damage	DNA strand breaks, comet assay	+	10 mg/L	Glyphosate, 48% Single dose tested only, for 24 h. The percentage of damaged DNA was 21% vs 4% (control) No statistical analysis	Mohamed (2011)
Oyster	Oysters, spermatozoa	DNA damage	DNA strand breaks, comet assay	–	5 µg/L	Glyphosate, 200 µg equivalent/L Time of exposure, 1 h	Akcha *et al.* (2012)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Clam	*Corbicula fluminea* (Asian clam) haemocytes	DNA damage	DNA strand breaks, comet assay	–	10 mg/L	Time of exposure, 96 h Significant increase when atrazine (2 or 10 mg/L) was added to glyphosate ($P < 0.05$) No increase after exposure to atrazine or glyphosate separately	dos Santos & Martinez (2014)
Mussels	*Utterbackia imbecillis* (Bivalvia: Unionidae) glochidia mussels (larvae)	DNA damage	DNA strand breaks, comet assay	–	5 mg/L	Glyphosate, 18% Doses tested: 2.5 and 5 mg/L for 24 h NOEC, 10.04 mg/L	Conners & Black (2004)
Worm	Earthworm, *Eisenia andrei*, coelomocytes	DNA damage	DNA strand breaks, comet assay	–	240 µg a.e./cm^2	Monoammonium salt, 85.4%, a.e. Epidermic exposure during 72 h (on filter paper)	Piola *et al.* (2013)
Worm	Earthworm, *Eisenia andrei*, coelomocytes	DNA damage	DNA strand breaks, comet assay	+	15 µg a.e./cm^2	Monoammonium salt, 72%, a.e. Epidermic exposure during 72 h (on filter paper) $P < 0.001$	Piola *et al.* (2013)
Worm	Earthworm, *Pheretima peguana*, coelomocytes	DNA damage	DNA strand breaks, comet assay	–	251.50 µg/cm^2	Active ingredient, 36% (w/v) Epidermic exposure 48 h on filter paper; LC_{50}, 251.50 µg/cm^2	Muangphra *et al.* (2014)
Worm	Earthworm, *Pheretima peguana*, coelomocytes	Chromosomal damage	Micronucleus formation	+	251.50 µg/cm^2	Active ingredient, 36% (w/v) Exposure, 48 h on filter paper; LC_{50}, 251.50 µg/cm^2 filterpaper $P < 0.05$, for total micro-, bi-, and trinuclei frequencies at 0.25 µg/cm^2; when analysed separately, micro- and trinuclei frequencies significantly differed from controls only at the LC_{50}	Muangphra *et al.* (2014)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Insect	*Drosophila melanogaster*	Mutation	Sex-linked recessive lethal mutations	+	1 ppm	Single dose tested only $P < 0.001$	Kale *et al.* (1995)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	+	1.44 µg/mL	Glyphosate-based formulation, 480 g/L The doses of formulation were calculated as glyphosate isopropylamine $P < 0.005$	Rank *et al.* (1993)
Plant systems	*Crepis capillaris* (hawksbeard)	Chromosomal damage	Chromosomal aberrations	–	0.5%	The highest dose tested (1%) was toxic	Dimitrov *et al.* (2006)
Plant systems	*Hordeum vulgare* L. cv. Madalin (barley roots)	Chromosomal damage	Chromosomal aberrations	(+)	360 µg/mL (0.1%)	Reported as "significant"	Truta *et al.* (2011)
Plant systems	*Crepis capillaris* (hawksbeard)	Chromosomal damage	Micronucleus formation	–	0.5%	The highest dose tested (1%) was toxic	Dimitrov *et al.* (2006)

[a] +, positive; –, negative; (+) or (–) positive/negative in a study with limited quality

a.e., acid equivalent; AMPA, aminomethyl phosphonic acid; bw, body weight; ENA, erythrocytic nuclear abnormalities; Endo III, endonuclease III; FPG, formamidopyrimidine glycosylase; h, hour; HID, highest ineffective dose; LC_{50}, median lethal dose; LED, lowest effective dose; NOEC, no-observed effect concentration; p.o., oral; SMART, somatic mutation and recombination test

Table 4.6 Genetic and related effects of glyphosate and glyphosate-based formulations on non-mammalian systems in vitro

Phylogenetic class	Test system (species; strain)	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Glyphosate								
Eukaryote Fish	*Oreochromis niloticus* (Nile tilapia), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	NT	7 µM [1.2 µg/mL]	Glyphosate isopropylamine, 96% $P \leq 0.001$; positive dose–response relationship for doses ≥ 7 µM	Alvarez-Moya et al. (2014)
Prokaryote (bacteria)	*Scytonema javanicum* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone; single dose tested only) enhanced UVB-induced increases	Wang et al. (2012)
Prokaryote (bacteria)	*Anabaena spherica* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone; single dose tested only) enhanced UVB-induced increases	Chen et al. (2012)
Prokaryote (bacteria)	*Microcystis viridis* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone; single dose tested only) enhanced UVB-induced increases	Chen et al. (2012)
Prokaryote (bacteria)	*Bacillus B. subtilis*	Differential toxicity	Rec assay	–	NT	2000 µg/disk		Li & Long (1988)
Prokaryote (bacteria)	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 and TA100	Mutation	Reverse mutation	–	–	5000 µg/plate		Li & Long (1988)
Prokaryote (bacteria)	*Escherichia coli* WP2	Mutation	Reverse mutation	–	–	5000 µg/plate		Li & Long (1988)

Table 4.6 (continued)

Phylogenetic class	Test system (species; strain)	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Acellular systems	Prophage superhelical PM2 DNA	DNA damage	DNA strand breaks	(–)	NT	75 mM [12.7 mg/mL] (in combination with H_2O_2 (100 µM)	Glyphosate inhibited H_2O_2-induced damage of PM2 DNA at concentrations where synergism was observed in cellular DNA damage (data NR)	Lueken et al. (2004)
Glyphosate-based formulations								
Prokaryote (bacteria)	*Salmonella typhimurium* TA98	Mutation	Reverse mutation	+	–	360 µg/plate	Glyphosate isopropylammonium salt, 480 g/L	Rank et al. (1993)
Prokaryote (bacteria)	*Salmonella typhimirium* TA100	Mutation	Reverse mutation	–	+	720 µg/plate	Glyphosate isopropylammonium salt, 480 g/L	Rank et al. (1993)

[a] +, positive; –, negative; (+) or (–) positive/negative in a study with limited quality

FADU, fluorometric analysis of DNA unwinding; HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested; UVB, ultraviolet B

Additionally, although all four glyphosate-based formulations dramatically reduced the transcription of ERα and ERβ in ERE-transfected HepG2 cells, glyphosate alone had no significant effect. Glyphosate and all four formulations reduced androgen-receptor transcription in the breast cancer cell line MDA-MB453-kb2, which has a high level of androgen receptor, with the formulations showing greater activity than glyphosate alone.

In a human placental cell line derived from choriocarcinoma (JEG3 cells), 18 hours of exposure to a glyphosate-based formulation (IC_{50} = 0.04%) decreased aromatase activity (Richard *et al.*, 2005). Glyphosate alone was without effect. The concentrations used did not affect cell viability.

Glyphosate, at non-overtly toxic concentrations, decreased aromatase activity in fresh human placental microsomes and transformed human embryonic kidney cells (293) transfected with human aromatase cDNA (Benachour *et al.*, 2007). A glyphosate-based formulation, at non-overtly toxic concentrations, had the same effect. The formulation was more active at equivalent doses than glyphosate alone.

In human androgen receptor and ERα and ERβ reporter gene assays using the Chinese hamster ovary cell line (CHO-K1), glyphosate had neither agonist nor antagonist activity (Kojima *et al.*, 2004, 2010).

(ii) Non-human mammalian experimental systems

In vivo

No data were available to the Working Group.

In vitro

Benachour *et al.* (2007) and Richard *et al.* (2005) reported that glyphosate and a glyphosate-based formulation inhibited aromatase activity in microsomes derived from equine testis. Richard *et al.* (2005) reported an absorbance spectrum consistent with an interaction between a nitrogen atom of glyphosate and the active site of the purified equine aromatase enzyme.

In the mouse MA-10 Leydig cell tumour cell line, a glyphosate-based formulation (glyphosate, 180 mg/L) markedly reduced $[(Bu)_2]$ cAMP-stimulated progesterone production (Walsh *et al.*, 2000). The inhibition was dose-dependent, and occurred in the absence of toxicity or parallel reductions in total protein synthesis. In companion studies, the formulation also disrupted steroidogenic acute regulatory protein expression, which is critical for steroid hormone synthesis. Glyphosate alone did not affect steroidogenesis at any dose tested up to 100 µg/L. Forgacs *et al.* (2012) found that glyphosate (300 µM) had no effect on testosterone production in a novel murine Leydig cell line (BLTK1). Glyphosate did not modulate the effect of recombinant human chorionic gonadotropin, which served as the positive control for testosterone production.

(iii) Non-mammalian experimental systems

Gonadal tissue levels of testosterone, 17β-estradiol and total microsomal protein were significantly reduced in adult snails (*Biomphalaria alexandrina*) exposed for 3 weeks to a glyphosate-based formulation (glyphosate, 48%) at the LC_{10} (10% lethal concentration) (Omran & Salama, 2013). These effects persisted after a 2-week recovery period, although the impact on 17β-estradiol was reduced in the recovery animals. The formulation also induced marked degenerative changes in the ovotestis, including absence of almost all the gametogenesis stages. CYP450 1B1, measured by enzyme-linked immunosorbent assay (ELISA), was substantially increased in the treated snails, including after the recovery period.

Glyphosate (0.11 mg/L for 7 days) did not increase plasma vittelogenin levels in juvenile rainbow trout (Xie *et al.*, 2005).

(b) Other pathways

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Glyphosate did not exhibit agonist activity in an assay for a human pregnane X receptor (PXR) reporter gene in a CHO-K1 cell line (Kojima *et al.*, 2010).

(ii) Non-human mammalian experimental systems

In vivo

In rats, glyphosate (300 mg/kg bw, 5 days per week, for 2 weeks) had no effect on the formation of peroxisomes, or the activity of hepatic carnitine acetyltransferase and catalase, and did not cause hypolipidaemia, suggesting that glyphosate does not have peroxisome proliferator-activated receptor activity (Vainio *et al.*, 1983).

In vitro

Glyphosate was not an agonist for mouse peroxisome proliferator-activated receptors PPARα or PPARγ in reporter gene assays using CV-1 monkey kidney cells in vitro (Kojima *et al.*, 2010). Glyphosate was also not an agonist for the aryl hydrocarbon receptor in mouse hepatoma Hepa1c1c7 cells stably transfected with a reporter plasmid containing copies of dioxin-responsive element (Takeuchi *et al.*, 2008).

(iii) Non-mammalian experimental systems

As a follow-up to experiments in which injection of glyphosate, or incubation with a glyphosate-based formulation (glyphosate, 48%), caused chick and frog (*Xenopus laevis*) cephalic and neural crest terata characteristic of retinoic acid signalling dysfunction, Paganelli *et al.* (2010) measured retinoic acid activity in tadpoles exposed to a glyphosate-based formulation. Retinoic activity measured by a reporter gene assay was increased by the formulation, and a retinoic acid antagonist blocked the effect. This indicated a possible significant modulation of retinoic acid activity by glyphosate.

4.2.3 Oxidative stress, inflammation, and immunosuppression

(a) Oxidative stress

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Several studies examined the effects of glyphosate on oxidative stress parameters in the human keratinocyte cell line HaCaT. Gehin *et al.* (2005) found that a glyphosate-based formulation was cytotoxic to HaCaT cells, but that addition of antioxidants reduced cytotoxicity. Elie-Caille *et al.* (2010) showed that incubation of HaCaT cells with glyphosate at 21 mM (the half maximal inhibitory concentration for cytotoxicity, IC_{50}) for 18 hours increased production of hydrogen peroxide (H_2O_2) as shown by dichlorodihydrofluorescein diacetate assay. Similarly, George & Shukla (2013) exposed HaCaT cells to a glyphosate-based formulation (glyphosate, 41%; concentration, up to 0.1 mM) and evaluated oxidative stress using the dichlorodihydrofluorescein diacetate assay. The formulation (0.1 mM) increased maximum oxidant levels by approximately 90% compared with vehicle, an effect similar to that of H_2O_2 (100 mM). Pre-treatment of the cells with the antioxidant *N*-acetylcysteine abrogated generation of oxidants by both the formulation and by H_2O_2. *N*-Acetylcysteine also inhibited cell proliferation induced by the glyphosate-based formulation (0.1 mM). [The Working Group noted the recognized limitations of using dichlorodihydrofluorescein diacetate as a marker of oxidative stress (Bonini *et al.*, 2006; Kalyanaraman *et al.*, 2012), and that the studies that reported this end-point as the sole evidence for oxidative stress should thus be interpreted with caution.]

Chaufan *et al.* (2014) evaluated the effects of glyphosate, AMPA (the main metabolite of glyphosate), and a glyphosate-based formulation on oxidative stress in HepG2 cells. The formulation, but not glyphosate or AMPA, had adverse effects. Specifically, the formulation increased levels of reactive oxygen species, nitrotyrosine formation, superoxide dismutase activity, and glutathione, but did not have an effect on catalase or glutathione-*S*-transferase activities. Coalova *et al.* (2014) exposed Hep2 cells to a glyphosate-based formulation (glyphosate as isopropylamine salt, 48%) at the LC_{20} (concentration not otherwise specified) and evaluated various parameters of oxidative stress. Exposure to the formulation for 24 hours increased catalase activity and glutathione levels, but did not have an effect on superoxide dismutase or glutathione-*S*-transferase activity.

Using blood samples from non-smoking male donors, Mladinic *et al.* (2009b) examined the effects of in-vitro exposure to glyphosate on oxidative DNA damage in primary lymphocyte cultures and on lipid peroxidation in plasma. Both parameters were significantly elevated at glyphosate concentrations of 580 µg/mL (~3.4 mM), but not at lower concentrations. Kwiatkowska *et al.* (2014) examined the effects of glyphosate, its metabolite AMPA, and *N*-methylglyphosate (among other related compounds) in human erythrocytes isolated from healthy donors. The erythrocytes were exposed at concentrations of 0.01–5 mM for 1, 4, or 24 hours before flow cytometric measurement of the production of reactive oxygen species with dihydrorhodamine 123. Production of reactive oxygen species was increased by glyphosate (≥ 0.25 mM), AMPA (≥ 0.25 mM), and *N*-methylglyphosate (≥ 0.5 mM).

(ii) Non-human mammalian experimental systems

Most of the studies of oxidative stress and glyphosate were conducted in rats and mice, and examined a range of exposure durations, doses, preparations (glyphosate and glyphosate-based formulations), administration routes and tissues. In addition, various end-points were evaluated to determine whether oxidative stress is induced by exposure to glyphosate. Specifically, it was found that glyphosate induces production of free radicals and oxidative stress in mouse and rat tissues through alteration of antioxidant enzyme activity, depletion of glutathione, and increases in lipid peroxidation. Increases in biomarkers of oxidative stress upon exposure to glyphosate in vivo have been observed in blood plasma (Astiz *et al.*, 2009b), liver (Bolognesi *et al.*, 1997; Astiz *et al.*, 2009b), skin (George *et al.*, 2010), kidney (Bolognesi *et al.*, 1997; Astiz *et al.*, 2009b), and brain (Astiz *et al.*, 2009b). Several studies demonstrated similar effects with a glyphosate-based formulation in the liver (Bolognesi *et al.*, 1997; Cavuşoğlu *et al.*, 2011; Jasper *et al.*, 2012), kidney (Bolognesi *et al.*, 1997; Cavuşoğlu *et al.*, 2011) and brain (Cattani *et al.*, 2014), or with a pesticide mixture containing glyphosate in the testes (Astiz *et al.*, 2013). Pre-treatment with antioxidants has been shown to mitigate the induction of oxidative stress by a glyphosate-based formulation (Cavuşoğlu *et al.*, 2011) and by a pesticide mixture containing glyphosate (Astiz *et al.*, 2013).

DNA damage associated with oxidative stress after exposure to glyphosate (e.g. as reported in Bolognesi *et al.*, 1997) is reviewed in Section 4.2.1.

(iii) Non-mammalian experimental systems

Positive associations between exposure to glyphosate and oxidative stress were reported in various tissues in aquatic organisms (reviewed in Slaninova *et al.*, 2009). Glyphosate and various glyphosate-based formulations have been tested in various fish species for effects on a plethora of end-points (e.g. lipid peroxidation, DNA damage, expression of antioxidant enzymes, levels of glutathione), consistently presenting evidence that glyphosate can cause oxidative stress in fish (Lushchak *et al.*, 2009; Ferreira *et al.*, 2010; Guilherme *et al.*, 2010, 2012a, b, 2014a, b; Modesto & Martinez, 2010a, b; Cattaneo *et al.*, 2011; Glusczak *et al.*, 2011; de Menezes *et al.*, 2011; Ortiz-Ordoñez *et al.*, 2011; Nwani *et al.*, 2013; Marques *et al.*, 2014, 2015; Sinhorin *et al.*, 2014; Uren Webster *et al.*, 2014). Similar effects were observed in bullfrog tadpoles exposed to a glyphosate-based formulation (Costa *et al.*, 2008), and in the Pacific oyster exposed to a pesticide mixture containing glyphosate (Geret *et al.*, 2013).

(b) Inflammation and immunomodulation

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Nakashima *et al.* (2002) investigated the effects of glyphosate on cytokine production in human peripheral blood mononuclear cells. Glyphosate (1 mM) had a slight inhibitory effect on cell proliferation, and modestly inhibited the production of IFN-gamma and IL-2. The production of TNF-α and IL-1β was not affected by glyphosate at concentrations that significantly inhibited proliferative activity and T-cell-derived cytokine production.

(ii) Non-human mammalian experimental systems

Kumar *et al.* (2014) studied the pro-inflammatory effects of glyphosate and farm air samples in wildtype C57BL/6 and $TLR4^{-/-}$ mice, evaluating cellular response, humoral response, and lung function. In the bronchoalveolar lavage fluid and lung digests, airway exposure to glyphosate (1 or 100 μg) significantly increased the total cell count, eosinophils, neutrophils, and IgG1 and IgG2a levels. Airway exposure to glyphosate (100 ng, 1 μg, or 100 μg per day for 7 days) also produced substantial pulmonary inflammation, confirmed by histological examination. In addition, glyphosate-rich farm-air samples significantly increased circulating levels of IL-5, IL-10, IL-13 and IL-4 in wildtype and in $TLR4^{-/-}$ mice. Glyphosate was also tested in wildtype mice and significantly increased levels of IL-5, IL-10, IL-13, and IFN-γ (but not IL-4). The glyphosate-induced pro-inflammatory effects were similar to those induced by ovalbumin, and there were no additional or synergistic effects when ovalbumin was co-administered with glyphosate.

Pathological effects of glyphosate on the immune system have been reported in 13-week rat and mouse feeding studies by the NTP (Chan & Mahler, 1992). Relative thymus weight was decreased in male rats exposed for 13 weeks, but increased in male mice. Treatment-related changes in haematological parameters were observed in male rats at 13 weeks and included mild increases in haematocrit [erythrocyte volume fraction] and erythrocytes at 12 500, 25 000, and 50 000 ppm, haemoglobin at 25 000 and 50 000 ppm, and platelets at 50 000 ppm. In female rats, small but significant increases occurred in lymphocyte and platelet counts, leukocytes, mean corpuscular haemoglobin, and mean corpuscular volume at 13 weeks.

Blakley (1997) studied the humoral immune response in female CD-1 mice given drinking-water containing a glyphosate-based formulation at concentrations up to 1.05% for 26 days. The mice were inoculated with sheep erythrocytes to produce a T-lymphocyte, macrophage-dependent antibody response on day 21 of exposure. Antibody production was not affected by the formulation.

(iii) Non-mammalian experimental systems

A positive association between exposure to glyphosate and immunotoxicity in fish has been reported. Kreutz *et al.* (2011) reported alterations in haematological and immune-system parameters in silver catfish (*Rhamdia quelen*) exposed to sublethal concentrations (10% of the median lethal dose, LC_{50}, at 96 hours) of a glyphosate-based herbicide. Numbers of blood erythrocytes, thrombocytes, lymphocytes, and total leukocytes were significantly reduced after 96 hours of exposure, while the number of immature circulating cells was increased. The phagocytic index, serum bacteria agglutination, and total peroxidase activity were significantly reduced after 24 hours of exposure. Significant decreases in serum bacteria agglutination and lysozyme activity were found after 10 days of exposure. No effect on serum bactericidal and complement natural haemolytic activity was seen after 24 hours or 10 days of exposure to glyphosate.

el-Gendy *et al.* (1998) demonstrated effects of a glyphosate-based formulation (glyphosate, 48%) at 1/1000 of the concentration recommended for field application on humoral and cellular immune response in bolti fish (*Tilapia nilotica*). The mitogenic responses of splenocytes to phytohaemagglutinin, concanavalin A, and lipopolysaccharide in fish exposed to glyphosate for 96 hours were gradually decreased and reached maximum depression after 4 weeks. Glyphosate also produced a concentration-dependent suppression of in-vitro plaque-forming cells in response to sheep erythrocytes.

4.2.4 Cell proliferation and death

(a) Humans

(i) Studies in exposed humans

No data were available to the Working Group.

(ii) Human cells in vitro

Cell proliferation potential was explored in HaCaT keratinocytes exposed to a glyphosate-based formulation (glyphosate, 41%; concentration, up to 0.1 mM) (George & Shukla, 2013). The formulation increased the number of viable cells, as assessed by the MTT assay (based on reduction of the dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) at concentrations up to 0.1 mM, while concentration- and incubation-time-dependent reductions were seen at higher concentrations (up to 1 mM). The formulation (0.01 or 0.1 mM for 72 hours) significantly enhanced cell proliferation (measured by staining for either proliferating cell nuclear antigen or 5-bromo-2′-deoxyuridine); at 0.1 mM, the increases exceeded levels for the positive control, tetradecanoyl-phorbol-13-acetate. The proportion of S-phase cells (assessed using flow cytometry) and the expression of G1/S cell-cycle regulatory proteins (cyclins D1 and E, CDK2, CDK4, and CDK6) increased after exposure to the formulation or the positive control.

Li *et al.* (2013) reported that glyphosate and AMPA inhibited cell growth in eight human cancer cell lines, but not in two immortalized normal prostate cell lines. An ovarian (OVCAR-3) and a prostate (C4–2B) cell line showed the greatest loss in viability, with glyphosate or AMPA at 15–50 mM. Further assays were conducted on AMPA, but not glyphosate, in two prostate cancer cell lines (C4–2B and PC-3), and found cell-cycle arrest (decreased entry of cells into S-phase) and increased apoptosis. [The Working Group noted that the findings from these assays with AMPA are of unclear relevance to the effects of glyphosate.]

Glyphosate (10^{-6} to 1 μM) increased growth by 15–30% relative to controls in hormone-dependent T47D breast cancer cells, but only when endogenous estrogen was minimized in the culture medium (by substitution with 10% dextran-charcoal treated fetal bovine serum). Glyphosate did not affect the growth of hormone-independent MDA-MB231 breast cancer cells cultured in either medium (Thongprakaisang *et al.*, 2013).

Glyphosate (up to 30 μM) did not show cell proliferation potential (5-bromo-2′-deoxyuridine) and did not activate caspase 3 or TP53 in human neuroprogenitor ReN CX cells (Culbreth *et al.*, 2012).

Several studies evaluated the impact of glyphosate or glyphosate-based formulations on apoptotic cell death in the HepG2 human hepatoma cell line. Glyphosate-based formulations induced apoptosis in HepG2 cells, while glyphosate alone was generally without effect or showed effects at considerably higher concentrations (Gasnier et al., 2009, 2010; Mesnage et al., 2013; Chaufan et al., 2014; Coalova et al., 2014). For example, 23.5% of the nuclei of HepG2 cells exposed to a glyphosate-based formulation showed condensed and fragmented chromatin ($P < 0.01$), and caspases 3 and 7 were significantly activated, both effects being indicative of apoptosis (Chaufan et al., 2014). Caspases were unaffected by glyphosate or AMPA alone. Glyphosate and AMPA did not affect cell viability at concentrations up to 1000 mg/L, a concentration that increased rather than decreased cell viability after 48 and 72 hours of incubation. In contrast, cells exposed to glyphosate-based formulation at lower concentrations were not viable. Similarly, Coalova et al. (2014) reported that a glyphosate-based formulation (glyphosate, 48%) induced apoptotic cell death in HepG2 cells. Apoptosis was indicated by activation of caspases 3 and 7, and the significant fraction (17.7%) of nuclei with condensed and fragmented chromatin ($P < 0.001$).

In studies with glyphosate and nine different glyphosate-based formulations in three cell lines, glyphosate alone did not increase the activity of adenylate kinase (Mesnage et al., 2013). The activity of caspases 3 and 7 was significantly increased by glyphosate in HepG2 and embryonic kidney HEK293 cells, and elevated (although not significantly) about 1.8 times above control levels in placental choriocarcinoma JEG-3 cells. Two formulations containing an ethoxylated adjuvant induced adenylate kinase activity to a greater extent than caspase activity. All formulations were reported to be more cytotoxic than glyphosate. [In concentration–response curves, glyphosate showed an effect on mitochondrial succinate dehydrogenase activity, a measure of cell viability, that was similar to that shown by one formulation. The calculated 50% lethal concentration in JEG3 cells for mitochondrial succinate dehydrogenase activity was greater for three formulations, although the values appeared inconsistent with the concentration–response curves.]

In HUVEC primary neonate umbilical cord vein cells, and 293 embryonic kidney and JEG3 placental cell lines, Benachour & Séralini (2009) found that glyphosate at relatively high concentrations induced apoptosis, as indicated by induction of caspases 3 and 7, and DNA staining and microscopy. At comparable or lower concentrations, four glyphosate-based formulations all caused primarily necrotic cell death. The umbilical cord HUVEC cells were the most sensitive (by about 100-fold) to the apoptotic effects of glyphosate.

Heu et al. (2012) evaluated apoptosis in immortalized human keratinocytes (HaCaT) exposed to glyphosate (5–70 mM). Based on annexin V, propidium iodide and mitochondrial staining, exposures leading to 15% cytotoxicity gave evidence of early apoptosis, while increases in late apoptosis and necrosis were observed at higher levels of cytotoxicity.

(b) Non-human mammalian experimental systems

(i) *In vivo*

In male Wistar rats, glyphosate (10 mg/kg bw, injected intraperitoneally three times per week for 5 weeks) reduced, but not significantly, the inner mitochondrial membrane integrity of the substantia nigra and cerebral cortex (Astiz et al. 2009a). Caspase 3 activity was unaltered in these tissues. Mitochondrial cardiolipin content was significantly reduced, particularly in the substantia nigra, where calpain activity was substantially higher. Glyphosate induced DNA fragmentation in the brain and liver.

(ii) In vitro

In adult Sprague Dawley rat testicular cells exposed in vitro, glyphosate (up to 1%; for 24 or 48 hours) did not provoke cell-membrane alterations (Clair *et al.*, 2012). However, caspase 3 and 7 activity increased with exposure in Sertoli cells alone, and in Sertoli and germ cell mixtures. On the other hand, a glyphosate-based formulation (a 0.1% solution, containing 0.36 g/L of glyphosate) induced membrane alterations and decreased the activity of caspase 3 and 7 in Leydig cells, and in Sertoli and germ cell mixtures. In a separate study, glyphosate increased apoptosis in primary Sertoli cell cultures from mice (Zhao *et al.*, 2013).

Glyphosate (5–40 mM, for 12, 24, 48, or 72 hours) significantly increased cell death in a time- and concentration-dependent manner in differentiated rat pheochromocytoma PC12 (neuronal) cells Gui *et al.* (2012). Apoptotic changes included cell shrinkage, DNA fragmentation, decreased Bcl2 expression, and increased Bax expression. Both autophagy and apoptosis were implicated, as pre-treatment with the pan-caspase inhibitor Z-VAD or the autophagy inhibitor 3-MA inhibited cell loss.

Induction of apoptosis by glyphosate or glyphosate-based formulations was also studied in other cell lines. Glyphosate (10 µM) induced apoptosis in rat heart H9c2 cells, the effect being enhanced when glyphosate was given in combination with the adjuvant TN-20 (5 µM), (Kim *et al.*, 2013). A glyphosate-based formulation induced apoptosis in mouse 3T3-L1 fibroblasts, and inhibited their transformation to adipocytes (Martini *et al.*, 2012). A glyphosate-based formulation (10 mM) did not increase rat hepatoma HTC cell death, but did affect mitochondrial membrane potential (Malatesta *et al.*, 2008).

Glyphosate (up to 30 µM) did not activate caspase 3 or show cell proliferation potential (5-bromo-2′-deoxyuridine) in a mouse neuroprogenitor cell line, but did activate Tp53 at the highest concentration tested (Culbreth *et al.*, 2012).

4.2.5 Other mechanisms

No data on immortalization, epigenetic alterations, altered DNA repair, or genomic instability after exposure to glyphosate were available to the Working Group.

4.3 Data relevant to comparisons across agents and end-points

No data on high-throughput screening or other relevant data were available to the Working Group. Glyphosate was not tested by the Tox21 and ToxCast research programmes of the government of the USA (Kavlock *et al.* 2012; Tice *et al.*, 2013).

4.4 Cancer susceptibility data

No studies that examined genetic, life-stage, or other susceptibility factors with respect to adverse health outcomes that could be associated with exposure to glyphosate were identified by the Working Group.

4.5 Other adverse effects

4.5.1 Humans

In the USA in the past decade, poison-control centres have reported more than 4000 exposures to glyphosate-containing herbicides, of which several hundred were evaluated in a health-care facility, and fatalities were rare (Rumack, 2015). In a pesticide surveillance study carried out by the National Poisons Information Service of the United Kingdom, glyphosate was among the most common pesticide exposure implicated in severe or fatal poisoning cases between 2004 and 2013 (Perry *et al.*, 2014). Deliberate poisonings with glyphosate resulting in toxicity and fatality have been reported in many countries, including Australia (Stella & Ryan, 2004), Denmark (Mortensen *et al.*, 2000), India (Mahendrakar *et al.*, 2014), Japan (Motojyuku *et al.*, 2008), Republic of Korea (Park *et al.*, 2013), New Zealand (Temple & Smith, 1992), Sri Lanka (Roberts *et al.*, 2010), Taiwan, China (Chen *et al.*, 2009), and Thailand (Sribanditmongkol *et al.*, 2012).

Glyphosate demonstrated no potential for photo-irritation or photo-sensitization in 346 volunteers exposed dermally on normal or abraded skin (Hayes & Laws, 1991). On the other hand, Mariager *et al.* (2013) reported severe burns after prolonged accidental dermal exposure to a glyphosate-based formulation.

4.5.2 Experimental systems

Glyphosate was tested in nine regulatory submissions included in the Toxicity Reference Database (ToxRefDB) and reviewed by the EPA (EPA, 2015). Specifically, study design, treatment group, and treatment-related effect information were captured for four long-term studies and/or carcinogenicity studies, one short-term study, two multigeneration studies of reproductivity, and two studies of developmental toxicity. The NTP also tested glyphosate in a 13-week study in rats and mice (Chan & Mahler, 1992).

In a long-term combined study of toxicity and carcinogenicity in rats given glyphosate at nominal doses of 100, 400, and 1000 mg/kg bw per day, inflammation was observed in the stomach mucosa of females at the intermediate and highest doses (EPA, 1990, 1991b). In males at the highest dose, liver weight, cataracts and lens degeneration in the eyes, and urine specific gravity were increased, while body weight, body-weight gain, and urinary pH were decreased. Pancreatic acinar cell atrophy was observed in males at the highest dose. Pancreatic inflammation was also observed in male rats at the highest dose in a short-term study (nominal doses of 50, 250, and 1000 mg/kg bw per day) (EPA, 1987). In the study by the NTP, cytoplasmic alteration was observed in the parotid and submandibular salivary glands of rats (Chan & Mahler, 1992).

In a study of carcinogenicity in mice given glyphosate at doses of 150, 1500, or 4500 mg/kg bw per day, liver hypertrophy and necrosis were observed in males at the highest dose (EPA, 1983). Other effects in males at the highest dose included increased testes weight, interstitial nephritis, and decreased body weight. In females at the highest dose, ovary weights were increased, proximal tubule epithelial basophilia and hypertrophy was observed, and body weights were decreased. In the study by the NTP, cytoplasmic alteration was observed in the parotid salivary glands in mice (Chan & Mahler, 1992).

Developmental and reproductive toxicity

In a study of developmental toxicity in rats given glyphosate at a dose of 300, 1000, or 3500 mg/kg bw per day, reduced implantation rates and fewer live fetuses were observed in dams at the highest dose (EPA, 1980b). In fetuses at the highest dose, unossified sternebra were observed and fetal weight was reduced.

5. Summary of Data Reported

5.1 Exposure data

Glyphosate is a broad-spectrum herbicide that is effective at killing or suppressing all plant types, including grasses, perennials, and woody plants. The herbicidal activity of glyphosate was discovered in 1970 and since then its use has increased to a point where it is now the most heavily used herbicide in the world, with an annual global production volume in 2012 of more than 700 000 tonnes used in more than 750 different products. Changes in farming practice and the development of genetically modified crops that are resistant to glyphosate have contributed to the increase in use.

There is little information available on occupational or community exposure to glyphosate. Glyphosate can be found in soil, air, surface water and groundwater, as well as in food. It has been detected in air during agricultural herbicide-spraying operations. Glyphosate was detected in urine in two studies of farmers in the USA, in urban populations in Europe, and in a rural population living near areas sprayed for drug eradication in Columbia. However, urinary concentrations were mostly below the limit of detection in several earlier studies of forestry workers who sprayed glyphosate. Exposure of the general population occurs mainly through diet.

5.2 Human carcinogenicity data

In its evaluation of the epidemiological studies reporting on cancer risks associated with exposure to glyphosate, the Working Group identified seven reports from the Agricultural Health Study (AHS) cohort and several reports from case–control studies. The AHS cohort, the pooled analyses of the case–control studies in the midwest USA, and the cross-Canada study were considered key investigations because of their relatively large size. Reports from two or more independent studies were available for non-Hodgkin lymphoma (NHL), multiple myeloma, Hodgkin lymphoma, glioma, and prostate. For the other cancer sites, results from only one study were available for evaluation.

5.2.1 NHL and other haematopoietic cancers

Two large case–control studies of NHL from Canada and the USA, and two case–control studies from Sweden reported statistically significant increased risks of NHL in association with exposure to glyphosate. For the study in Canada, the association was seen among those with more than 2 days/year of exposure, but no adjustment for other pesticides was done. The other three studies reported excesses for NHL associated with exposure to glyphosate, after adjustment for other pesticides (reported odds ratio were 2.1 (95% CI, 1.1–4.0); 1.85 (95% CI, 0.55–6.2); and 1.51 (95% CI, 0.77–2.94). Subtype-specific analyses in a Swedish case–control study indicated positive associations for total NHL, as well as all subtypes, but this association was statistically significant only for the subgroup of lymphocytic lymphoma/chronic lymphocytic leukaemia (OR, 3.35; 95% CI, 1.42–7.89). An elevated risk (OR, 3.1; 95% CI, 0.6–17.1) was also found for B-cell lymphoma in an European study based on few cases. One hospital-based case–control study from France did not find an association between exposure to glyphosate and NHL (OR, 1.0; 95% CI, 0.5–2.2) based on few exposed cases.

A roughly twofold excess of multiple myeloma, a subtype of NHL, was reported in three studies: only among the highest category of glyphosate use (> 2 days/year) in the large Canadian case–control study, in a case–control study from Iowa, USA, and in a French case–control study (all not statistically significant). These three studies did not adjust for the effect of other pesticides. In the AHS, there was no association with NHL (OR, 1.1; 0.7–1.9). For multiple myeloma, relative risk was 1.1 (95% CI, 0.5–2.4) when adjusted for age only; but was 2.6 (95% CI, 0.7–9.4) when adjusted for multiple confounders. No excess in leukaemia was observed in a case–control study in Iowa and Minnesota, USA, or in the AHS.

In summary, case–control studies in the USA, Canada, and Sweden reported increased risks for NHL associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. The AHS cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the risk estimates were statistically significant nor were they adjusted for other pesticide exposures.

5.2.2 Other cancer sites

No association of glyphosate with cancer of the brain in adults was found in the Upper Midwest Health case–control study. No associations in single case–control studies were found for cancers of the oesophagus and stomach, prostate, and soft-tissue sarcoma. For all other cancer sites (lung, oral cavity, colorectal, pancreas, kidney, bladder, breast, prostate, melanoma) investigated in the large AHS, no association with exposure to glyphosate was found.

5.3 Animal carcinogenicity data

Glyphosate was tested for carcinogenicity in male and female mice by dietary administration in two studies, and in male and female rats by dietary administration in five studies and in drinking-water in one study. A glyphosate-based formulation was also tested in drinking-water in one study in male and female rats, and by skin application in one initiation–promotion study in male mice.

There was a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. Renal tubule carcinoma is a rare tumour in this strain of mice. No significant increase in tumour incidence was seen in female mice in this study. In the second feeding study, there was a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice. No significant increase in tumour incidence was seen in female mice in this study.

For the five feeding studies in rats, two studies in the Sprague-Dawley strain showed a significant increase in the incidence of pancreatic islet cell adenoma in males – one of these two studies also showed a significant positive trend in the incidences of hepatocellular adenoma in males and of thyroid C-cell adenoma in females. Two studies (one in Sprague-Dawley rats, one in Wistar rats) found no significant increase in tumour incidence at any site. One study in Wistar rats was inadequate for the evaluation because of the short duration of exposure.

In the study in Wistar rats given drinking-water containing glyphosate, there was no significant increase in tumour incidence.

A glyphosate-based formulation was found to be a skin-tumour promoter in the initiation–promotion study in male Swiss mice. The study of a glyphosate-based formulation in drinking-water in Sprague-Dawley rats was inadequate for the evaluation because of the small number of animals per group, and the limited information provided on tumour histopathology and incidence in individual animals. These studies of a chemical mixture containing glyphosate were considered inadequate to evaluate the carcinogenicity of glyphosate alone.

5.4. Other relevant data

Direct data on absorption of glyphosate in humans were not available to the Working Group. Glyphosate was detected in the urine of agricultural workers in several studies, and in the blood of poisoning cases, indicative of absorption. Some evidence for absorption through human skin (~2%) was reported in studies in vitro. The minor role of dermal absorption was also shown in a study in non-human primate model in vivo. However, no study examined the rates of absorption in humans. In rodents, several studies showed up to 40% absorption after oral administration of a single or repeated dose.

Glyphosate was measured in human blood. No data on parenchymal tissue distribution for glyphosate in humans were available to the Working Group. In rats given glyphosate by oral administration, concentrations in tissues had the following rank order: kidneys > spleen > fat > liver. Repeated administration had no effect on the distribution of glyphosate. In a study in rats, the half-life of glyphosate in plasma was estimated to be more than 1 day, indicating that glyphosate is not rapidly eliminated.

In the environment, glyphosate is degraded by soil microbes, primarily to aminomethylphosphonic acid (AMPA) and carbon dioxide. Glyphosate is not efficiently metabolized in humans or other mammals. In rats, small amounts of AMPA were detected in the plasma and in the colon, with the latter being attributed to intestinal microbial metabolism. In humans, small amounts of AMPA are detectable in blood in cases of deliberate glyphosate poisoning. Few studies examined the possible effects of glyphosate-based formulations on metabolizing enzymes, but no firm conclusions could be drawn from these studies.

Studies in rodents showed that systemically absorbed glyphosate is excreted unchanged into the urine, and that the greatest amount is excreted in the faeces, indicating poor absorption. Glyphosate was detected in the urine of humans who were exposed occupationally to glyphosate. AMPA has also been detected in human urine.

Glyphosate is not electrophilic.

A large number of studies examined a wide range of end-points relevant to genotoxicity with glyphosate alone, glyphosate-based formulations, and AMPA.

There is strong evidence that glyphosate causes genotoxicity. The evidence base includes studies that gave largely positive results in human cells in vitro, in mammalian model systems in vivo and in vitro, and studies in other non-mammalian organisms. In-vivo studies in mammals gave generally positive results in the liver, with mixed results for the kidney and bone marrow. The end-points that have been evaluated in these studies comprise biomarkers of DNA adducts and various types of chromosomal damage. Tests in bacterial assays gave consistently negative results.

The evidence for genotoxicity caused by glyphosate-based formulations is strong. There were three studies of genotoxicity end-points in community residents exposed to glyphosate-based formulations, two of which reported positive associations. One of these studies examined chromosomal damage (micronucleus formation) in circulating blood cells before and after aerial spraying with glyphosate-based formulations and found a significant increase in micronucleus formation after exposure in three out of four different geographical areas. Additional evidence came from studies that gave largely positive results in human cells in vitro, in mammalian model systems in vivo and in vitro, and studies in other non-mammalian organisms. The end-points that were evaluated in these studies comprised biomarkers of DNA adducts and various types of chromosomal damage. The pattern of tissue specificity of genotoxicity end-points observed with glyphosate-based formulations is similar to that observed with glyphosate alone. Tests in bacterial assays gave generally negative results.

For AMPA, the evidence for genotoxicity is moderate. While the number of studies that examined the effects of AMPA was not large, all of the studies gave positive results. Specifically, genotoxicity was reported in a study in humans in vitro, a study in mammals in vivo, a study in mammals in vitro, and one study in eels in vivo.

Strong evidence exists that glyphosate, AMPA, and glyphosate-based formulations can induce oxidative stress. Evidence came from studies in many rodent tissues in vivo, and human cells in vitro. In some of these studies, the mechanism was challenged by co-administration of antioxidants and observed amelioration of the effects. Similar findings have been reported in fish and other aquatic species. Various end-points (e.g. lipid peroxidation markers, oxidative DNA adducts, dysregulation of antioxidant enzymes) have been evaluated in numerous studies. This increased the confidence of the Working Group in the overall database.

There is weak evidence that glyphosate or glyphosate-based formulations induce receptor-mediated effects. In multiple experiments, glyphosate-based formulations affected aromatase activity; glyphosate was active in a few of these studies. Some activity in other nuclear receptor-mediated pathways has been observed for glyphosate or glyphosate-based formulations. In one series of experiments, glyphosate was not found to be a ligand to several receptors and related proteins (aryl hydrocarbon receptor, peroxisome proliferator-activated receptors, pregnane X receptor).

There is weak evidence that glyphosate may affect cell proliferation or death. Several studies in human and rodent cell lines have reported cytotoxicity and cell death, the latter attributed to the apoptosis pathway. Studies that examined the effects of glyphosate alone or a glyphosate-based formulation found that glyphosate alone had no effect, or a weaker effect than the formulation.

There is weak evidence that glyphosate may affect the immune system, both the humoral and cellular response, upon long-term treatment in rodents. Several studies in fish, with glyphosate or its formulations, also reported immunosuppressive effects.

With regard to the other key characteristics of human carcinogens (IARC, 2014), the Working Group considered that the data were too few for an evaluation to be made.

Severe or fatal human poisoning cases have been documented worldwide. In rodents, organ and systemic toxicity from exposures to glyphosate are demonstrated by liver-weight effects and necrosis in animals at high doses. Additionally, effects on the pancreas, testes, kidney and ovaries, as well as reduced implantations and unossified sternebra were seen at similar doses.

No data on cancer-related susceptibility after exposure to glyphosate were available to the Working Group.

Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate.

6.3 Overall evaluation

Glyphosate is *probably carcinogenic to humans (Group 2A).*

6.4 Rationale

In making this overall evaluation, the Working Group noted that the mechanistic and other relevant data support the classification of glyphosate in Group 2A.

In addition to limited evidence for the carcinogenicity of glyphosate in humans and sufficient evidence for the carcinogenicity of glyphosate in experimental animals, there is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens, and that these can be operative in humans. Specifically:

- There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals.

One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation) were significantly greater after exposure than before exposure in the same individuals.

- There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress.

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From: Akerman, Gregory
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate CARC - Preparation
Start Date/Time: Thur 7/30/2015 3:00:00 PM
End Date/Time: Thur 7/30/2015 4:00:00 PM

From: Akerman, Gregory
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate CARC - Preparation
Start Date/Time: Wed 7/29/2015 2:00:00 PM
End Date/Time: Wed 7/29/2015 3:00:00 PM

From: Akerman, Gregory
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate CARC - Preparation
Start Date/Time: Wed 7/29/2015 1:00:00 PM
End Date/Time: Wed 7/29/2015 2:00:00 PM

From: Akerman, Gregory
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Akerman, Gregory
Sent: Tue 5/26/2015 1:59:36 PM
Subject: RE: Glyphosate CARC Meeting

The 8TH is fine for me

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
Subject: Glyphosate CARC Meeting

We are considering moving the CARC meeting on Glyphosate from June 24th to July 8th. Please let me know ASAP if you CANNOT make the July 8th meeting date.

Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Akerman, Gregory
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

From: Nguyen, Khue
Location: DCRoomPYS9621/Potomac-Yard-One
Importance: Normal
Subject: confirmed: glyphosate call with Monsanto re inerts info request
Start Date/Time: Tue 4/5/2016 7:00:00 PM
End Date/Time: Tue 4/5/2016 8:00:00 PM

We are calling Monsanto to get additional information for HED's inerts info request. The focus is on inerts info that is not already available in house--including info for European formulations and info on inerts used in the 90s.

Thanks,
Khue

From: Nguyen, Khue
Location: DCRoomPYS9100/Potomac-Yard-One
Importance: Normal
Subject: glyphosate: meeting with Monsanto
Start Date/Time: Thur 6/4/2015 5:00:00 PM
End Date/Time: Thur 6/4/2015 6:00:00 PM

Monsanto has requested a meeting with the team to have a broad high level discussion concerning registration review. List of the discussion topics in chain below. We have made it clear to Monsanto that we are not in a position to discuss the weed resistance management language that they sent (I don't think the team has had a chance to look at it yet), new developments on the pollinator front, the IARC report and our response, the breast milk study, etc because everything is very much draft, internal, and deliberative. But from the gist of my conversation with Monsanto, they want to talk at us, and they want some of the experts (from BEAD, HED, and EFED) in the room to hear them.

I know this is very last minute, whoever is available tomorrow can come, I don't expect that everyone can be available.

Thanks,
Khue

Call-in information:
Dial in num: Ex. 6 - Personal Privacy
Conference code: Ex. 6 - Personal Privacy

Hi Khue

We'd like to discuss:

Our final paired urine/human milk test results **(they are sharing their results with EPA prior to publication)**

Endangered species analysis

Monarchs

WRM proposals for glyphosate

Comment period timing

Thanks,

Dan Jenkins
US Agency Lead
Monsanto Company
202.383.2851 office

571.732.6575 cell

To: Goodis, Michael[Goodis.Michael@epa.gov]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]
From: Nguyen, Khue
Sent: Fri 5/6/2016 2:48:51 PM
Subject: RE: Glyphosate CARC
glyphosate cancer reassessment 10.1.15.pdf

Please see attached. Thx.

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: Goodis, Michael
Sent: Friday, May 06, 2016 10:47 AM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>
Subject: Glyphosate CARC

Khue

When you get a chance, would you mind sending me the CARC report so I can read it?

I expect to get some questions on it during my next OECD meeting in June so would like to familiarize myself with what is in it. Thanks

Michael Goodis, P.E.

Associate Director, Pesticide Re-evaluation Division (PRD)

Office of Pesticide Programs

Phone 703-308-8157

Mail code 7508P

Room S9624

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **October 1, 2015**

SUBJECT: **GLYPHOSATE:** Report of the Cancer Assessment Review Committee

PC Code: 417300	**DP Barcode:** N/A
Decision No.: N/A	**Registration No.:** N/A
Petition No.: N/A	**Regulatory Action:** N/A
Risk Assessment Type: NA	**Case No.:** N/A
TXR No.: 0057299	**CAS No.:** 1071-83-6
MRID No.: N/A	**40 CFR:** N/A

FROM: Jess Rowland, Jess Rowland
Deputy Division Director
Chair, Cancer Assessment Review Committee
And
Karlyn Middleton, Co-Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Charles Smith, Chief,
Risk Assessment Branch I
Health Effects Division (7509P)
And
Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division

On September 16, 2015, the Cancer Assessment Review Committee (CARC) of the Health Effects Division, of the Office of Pesticide Programs evaluated the carcinogenic potential of Glyphosate in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
Glyphosate

FINAL REPORT
October 1, 2015

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S Environmental Protection Agency

Table of Contents

COMMITTEE MEMBERS IN ATTENDANCE:

Jess Rowland, M.S., Chair

Karlyn Middleton, M.S., Co-Chair

Gregory Akerman, Ph.D.

Lori Brunsman, B.S.

Jonathan Chen, Ph.D.

Anwar Dunbar, Ph.D.

Ray Kent, Ph.D.

Jessica Kidwell, M.S.

John Liccione, Ph.D.

Dannelle Lobdell, Ph.D., Epidemiologist, ORD

Nancy McCarroll, M.S.

Chris Schlosser, M.S.

Charles Wood D.V.M., Ph.D., Pathologist, ORD

EXECUTIVE SUMMARY

Glyphosate is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division (HED), of the Office of Pesticide Programs (OPP), of the U.S. Environmental Protection Agency (USEPA) evaluated the carcinogenic potential of glyphosate. In accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* the CPRC classified glyphosate as a Group E Chemical: "Evidence of Non-Carcinogenicity for Humans" based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008897).

Earlier this year (March 2015), the International Agency for Research on Cancer (IARC), Lyon, France, assessed the carcinogenic potential of glyphosate. The IARC reviewed the available epidemiological studies and carcinogenicity studies for glyphosate in experimental animals. The IARC concluded that there is *limited evidence* in humans for the carcinogenicity of glyphosate based on a positive association for non-Hodgkin lymphoma (NHL). The IARC also concluded that there is *sufficient evidence* in experimental animals based on significant positive trends for kidney tumors in one study and for hemangiosarcomas in another study in male mice. IARC determined that there is strong evidence for genotoxicity. Overall, IARC classified glyphosate as "*probably carcinogenic to humans (Group 2A)* (IARC, 2015).

IARC's conclusion was based on epidemiologic studies available in the open literature and carcinogenicity studies in rats (4 studies) and mice (2 studies) by dietary administration. Of these six studies reviewed by IARC, two studies in rats and one study in mice were previously not available to OPP. The conclusion by IARC and the additional studies not available to OPP, prompted the agency to re-evaluate the carcinogenic potential of glyphosate.

On September 16, 2015, HED's Cancer Assessment Review Committee (CARC) evaluated all available epidemiological studies published in the open literature that examined the association between glyphosate exposure and one or more cancer outcomes. This included one cohort study, seven nested case-control studies based on the cohort study population, and 25 case- control studies. The CARC also evaluated 11 chronic toxicity/carcinogenicity studies in rats (7) and mice (4) following dietary administration for up to two years. Six of the studies (4 rat and 2 mouse) were submitted to OPP to support registration/re-registration requirements, including two studies in rats and one study in mice which were not previously available to OPP (but reviewed by IARC). Data for review of the other five studies (3 rat and 2 mouse) were obtained from a review article and its supplement published in the open literature (Greim *et al.,* 2015) that also had not been previously reviewed by the agency (IARC did not evaluate the five studies cited in the Greim *et al.* 2015 review article). The CARC also evaluated the mutagenicity/genotoxicity studies submitted to OPP as well as studies summarized in two review articles (Williams *et al*., 2000, and Kier and Kirkland, 2013) published in the open literature.

The CARC concluded that the epidemiological studies in humans showed no association between glyphosate exposure and cancer of the following: oral cavity, esophagus, stomach, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, brain (gliomas), soft-tissue sarcoma, leukemia, or multiple myelomas.

The CARC concluded that there is conflicting evidence for the association between glyphosate exposure and NHL. No association between glyphosate exposure and NHL was found in population-based case-control studies in the United States, Canada or France. Additionally, the large prospective Agricultural Health Study (AHS) with 54,315 licensed pesticide applicators in Iowa and North Carolina did not show a significantly increased risk of NHL. A population-based case-control study from Sweden suggested an association between glyphosate exposure and NHL; however, this finding was based on only 4 glyphosate-exposed cases and 3 controls.

When data from two case-control studies in Sweden (one on NHL and the other on hairy cell leukemia) were pooled, a univariate analysis showed an increased risk (odds ratio (OR) = 3.04; 95% confidence interval (CI) = 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, the risk was attenuated (OR=1.85; 95% CI=0.55–6.20). In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analysis showed an increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51). A meta-analysis of the six separate studies showed an association between glyphosate exposure and NHL with a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014). The CARC noted that most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and had risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data.

In an attempt to address the noted power/sample size issues across studies, IARC used adjusted weighting estimates of the two Swedish studies (Hardell *et al*. 2002 and Eriksson *et al*. 2008) and reported an lower odds ratio in a second meta-analysis of the same data (OR=1.3; 95% CI=1.03–1.65). Given the limitations of the studies used and uncertainty in the analytical methods, the CARC concluded that a different weighting scheme could have resulted in a different meta risk ratio. Thus, while epidemiologic literature to date does not support a direct causal association, the CARC recommends that the literature should continue to be monitored for studies related to glyphosate and risk of NHL.

Overall, the CARC concluded that there was no evidence of carcinogenicity in the eleven carcinogenicity studies conducted in Sprague Dawley or Wistar rats and CD-1 mice. There were no treatment-related increases in the occurrence of any tumor type in either sex of either species.

By contrast, the IARC concluded that there is *sufficient evidence* in experimental animals based on a positive trend in the incidence of a relatively rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in CD-1 males in one feeding study. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. The CARC did not consider these tumors to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported non-neoplastic changes, were not statistically significant on pairwise analysis with concurrent control groups, and/or were within the range of the historical control data. If the kidney tumors and the hemangiosarcomas are really treatment-related, it is unlikely that the same tumors would not have been detected at higher incidences in the studies in the other studies of CD-1 mice when tested at similar or higher doses (1000–4000 mg/kg/day). Moreover, in 4 of the 11 studies (3 rat and 1 mouse) evaluated by CARC, there was no biologically or statistically significant increases in the occurrence of any tumor type in either species. The other observed differences in incidence did not show a dose response relationship, and were within the range of the background/historical control range. The four studies which were negative for carcinogenicity were reported in the review article by Greim *et al.* (2015) but were not included in the IARC evaluation. This omission of the negative findings from reliable studies may have had a significant bearing on the conclusion drawn for evidence of carcinogenicity in animals.

The CARC evaluated a total of 54 mutagenicity/genotoxicity studies which included studies submitted to the agency, as well as studies reported in the two review articles (Williams *et al*., 2000, and Kier and Kirkland, 2013). A number of studies reported in the review article by Kier and Kirkland (2013) were not considered by IARC. The CARC, based on a weight-of-evidence of the *in vitro* and *in vivo* studies, concluded that there is no concern for genotoxicity or mutagenicity. Glyphosate was no mutagenic in bacterial reversion (Ames) assays or *in vitro* mammalian gene mutation assays. There is no convincing evidence that glyphosate induces micronuclei formation or chromosomal aberrations *in vitro* or *in vivo*.

By contrast, IARC's conclusion that glyphosate is genotoxic based on positive results that included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e*., no purity information was provided). The IARC analysis also focused on DNA damage as an endpoint (*e.g*., comet assay). DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited as positive findings for chromosomal damage had deficiencies in the design and/or conduct of the studies confounding the interpretation of the results. In addition these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. Furthermore, IARC's evaluation did not include a number of negative results from studies that were reported in the review article by Kier and Kirkland (2013). The inclusion of the positive findings from studies with known limitations, the lack of reproducible positive findings and the omission of the negative findings from reliable studies may have had a significant bearing on IARC's conclusion on the genotoxic potential of glyphosate.

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, based on the weight-of-evidence, glyphosate is classified as "Not Likely to be Carcinogenic to Humans". This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk/odd ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis with concurrent control groups, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

I. INTRODUCTION

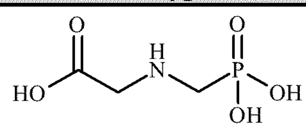
On September 16, 2015 the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of glyphosate.

II. BACKGROUND INFORMATION

Glyphosate (*N*-(phosphonomethyl) glycine) is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Tolerances are currently established for residues of glyphosate in/on various plant commodities at 0.2–400 ppm (40 CFR §180.364 (a)) (1). Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way.

The chemical structure and nomenclature for glyphosate is presented in Table 1.

Table 1. Chemical Nomenclature of Glyphosate

Compound	
Common name	Glyphosate
Company experimental name	DPX-B2856
IUPAC/CAS name	*N*-(phosphonomethyl)glycine
CAS registry number	1071-83-6

Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment. Application rates of glyphosate to food crops range from <1 pound (lb) of acid equivalent (ae) per acre (A) for a variety of crops to approximately 15 lb ae/A for spray and spot treatments of crops including tree nuts, apples, citrus, and peaches. Residential lawn and turf application rates range from <1 lb ae/A to approximately 10.5 lb ae/A. The application timing of glyphosate is varied. Glyphosate can be applied early and late in the season, at pre-plant, planting, pre-emergence, pre-bloom, bud stage, pre-transplant, pre-harvest, post-plant, post-transplant, post-bloom, and post-harvest. It can also be applied during dormant stages and to fallow land, established plantings, stubble, and when needed. In September 1993, the agency issued the glyphosate Reregistration Eligibility Decision (RED) document (D362745), available from http://www.epa.gov/pesticides/reregistration/REDs/old_reds/glyphosate.pdf.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division, Office of Pesticide Programs, in accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* classified glyphosate as a Group E Chemical: Evidence of Non-Carcinogenicity for Humans. This classification was based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR No. 0008897).

In 2002, the European Union (EU) concluded that there was no evidence of carcinogenicity for glyphosate in long-term studies with mice and rats (EU, 2002).

In 2004, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that there was no evidence of carcinogenicity for glyphosate in long term studies in mice and rats and there was no evidence for genotoxic potential (JMPR, 2004).

In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as a Group 2A chemical (Probable Human Carcinogen) based on *limited evidence* of carcinogenicity in humans and sufficient evidence in experimental animals. The limited evidence in humans was based on a positive association between non-Hodgkin lymphoma (NHL) and glyphosate exposure from published epidemiology studies. The *sufficient evidence* in experimental animals was based on a positive trend in the incidence of renal tubular carcinoma and renal tubule adenoma/ carcinoma combined in male CD-1 mice in one study and on a positive trend in the incidence of hemangiosarcomas in male CD-1 mice in another study. There is strong evidence that glyphosate causes genotoxicity (IARC, 2015).

In 2015, two chronic toxicity/carcinogenicity studies in rats (MRID Nos. 49631701; 4970460) and one carcinogenicity study in mice (MRID No. 49631702) that were reviewed by IARC, but not previously available to OPP, were submitted and reviewed. This assessment by the CARC includes all of the studies (epidemiology and animals) reviewed by IARC as well as a subset of animal studies reported in a review article by Greim *et al.* (2015) but not reviewed by IARC.

III. EPIDEMIOLOGY

This section includes a review of epidemiologic cohort and case-control studies of glyphosate to evaluate whether exposure to glyphosate is associated causally with the risk of developing cancer in humans.

The Agricultural Health Study (AHS) is a large prospective study conducted in Iowa and North Carolina. Participants (private and commercial applicators) were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire (Alavanja *et al.,* 1996). The role of pesticide use and lymph hematopoietic cancers, and in particular NHL, has been studied in several investigations. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available (De Roos *et al*., 2005); however, for NHL and other non-solid tumors, several investigations are published.

A. Cohort Study

There are multiple published studies which use data from the same cohort, the AHS (Alavanja *et al.,* 2003; Flower *et al*., 2004; De Roos *et al*., 2005; Engel *et al*., 2005; Lee *et al*., 2007; Landgren *et al*., 2009; Andreotti *et al*., 2009; and Dennis *et al*., 2010). It should be noted that there is some overlap between the cases and person-time reported findings in the AHS.

B. Case-Control Studies

Three case-control studies conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s were reported by Brown *et al.* (1990), Cantor *et al.* (1992) and Brown *et al.* (1993).

De Roos *et al.* (2003) and Lee *et al.* (2004a) reported the results of case-control studies conducted in Iowa, Minnesota, Nebraska and/or Kansas in the U.S.A.

The Canadian population based case-control studies were reported by McDuffie *et al*., 2001; Hohenadel *et al*., 2011; Karunanayke *et al*., 2012; and Kachuri *et al*., 2013.

Results of the Swedish case-control studies were reported by Nordstrom *et al.*, 1998; Hardell and Erikson, 1999 and Hardell *et al*., 2002; and Eriksson *et al*., 2008.

A single case-control study conducted in France was reported by Orsi *et al.* (2009).

Coco *et al.*, (2013) reported the results of a pooled analyses of case-control studies conducted in six European countries between 1998 and 2004.

Case-control studies on the cancer of the brain (mainly gliomas) were reported by Ruder *et al.* 2004; Carreon *et al.*, 2005; Lee *et al.*, 2005; and Yiin *et al.*, 2012.

Case-control studies on other cancer sites were reported by Alavanja *et al.*, 2004 (lung); Bank *et al.*, 2011 and Koutros *et al.*, 2013 (prostate); Pahwa *et al.*, 2012 (soft tissue sarcoma) and Lee *et al.,* 2004b (stomach and esophagus).

Schinasi and Leon (2014) conducted a meta-analysis of the six studies that evaluated NHL and glyphosate exposure (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; DeRoos *et al.*, 2003; 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Sorahan (2015) conducted a re-analysis of the multiple myeloma in the U.S. AHS.

C. Results

A summary of the studies evaluating the association between glyphosate exposure and cancer are discussed below.

- Results of the studies reporting data on solid tumors (non-lymphohematopoietic) at various anatomical sites are presented in Table 2.

- Results of the studies reporting data on glyphosate exposure and non-solid tumors (lymphohematopoietic) are presented in Table 3.

1. Solid Tumor Cancer Studies

Within the AHS study cohort, a number of authors evaluated several anatomical cancer sites in relation to pesticide use. A discussion of studies outside of the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in Section C.2. (Non-Solid Tumor Sites).

(i) Cancer at Multiple Sites

De Roos *et al.*, (2005) evaluated associations between glyphosate exposure and cancer incidence in the AHS cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. The authors used Poisson regression to estimate exposure-response relationships between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Exposure to glyphosate was not associated with all cancers combined [Rate Ratio (RR) =1.0 with 95% Confidence Interval (CI) of 0.90–1.2)] or any cancer at a specific anatomical site.

Several AHS nested case-control analyses as well as the cohort analysis from De Roos *et al.*, 2005, also provide information concerning the carcinogenic potential of glyphosate. As presented in Table 2, there is no statistical evidence of an association with glyphosate presented across these studies. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al.*, 2005), colon (De Roos *et al.*, 2005; Lee *et al.*, 2007), rectum (De Roos *et al.*, 2005; Lee *et al.*, 2007), lung (De Roos *et al.*, 2005), kidney (De Roos *et al.*, 2005), bladder (De Roos *et al.*, 2005), pancreas (De Roos *et al.*, 2005; Andreotti *et al.*, 2009), breast (Engel *et al.*, 2005), prostate (Alavanja *et al.*, 2003; Koutros *et al.*, 2013) or melanoma (De Roos *et al.*, 2005; Dennis *et al.*, 2010). The risk ratios (OR) or rate ratios (RR) and 95% confidence interval (CI) for these studies are provided in Table 2.

In a population-based study (Band *et al.*, 2011) outside of the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI=0.83–2.25). This study included prostate cancer cases from 1983-1990, prior to the prostate-specific antigen (PSA) era. Consequently, the study included more advanced tumors before diagnosis. Additionally, these data are in conflict with the results of Alavanja *et al.* (2003), which reflects the PSA-era cases (*i.e.*, cases which are typically identified at an earlier stage in the progression of the disease). Koutros *et al.* (2013) did not identify an association with advanced prostate cancer (OR=0.93; 95% CI=0.73–1.18) in a prostate cancer follow-up study within the AHS.

A Canadian case-control study (Pahwa *et al.*, 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with the use of glyphosate (OR=0.90; 95% CI= 0.58–1.40).

Flower *et al.* (2004) examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate (OR=0.61; 95% CI= 0.32–1.16) or paternal (prenatal) exposure to glyphosate: (OR=0.84; 95% CI= 0.35– 2.54).

(ii) <u>Brain (Glioma) Cancer</u>

Lee *et al.* (2005) investigated the association between brain cancer with farming and agricultural pesticide use. The authors conducted telephone interviews of men and women diagnosed with gliomas (n=251) between 1988 and 1993 in Nebraska and in controls (n=498) identified from the same regions. Matching for age and vital status, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI=0.7–3.1) in relation to glyphosate use; however, the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI=0.1–1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2–8.2), indicating recall bias was likely a characteristic of this study.

Three population-based case-control studies evaluated the risk of brain cancer, specifically, glioma risk, among men and women participating in the Upper Midwest Health Study (Carreon *et al.*, 2005; Ruder *et al.*, 2004; Yiin *et al.*, 2012). Ruder *et al.* (2004) reported no association between brain cancer and glyphosate use, but did not present any specific results (*i.e.* quantitative data). Among glioma cases identified 1995–1997 by Carreon *et al.* (2005), the authors found little evidence of a role for glyphosate in the etiology of this tumor. Herbicide use, including glyphosate was not associated with glioma in women by proxy respondents (OR=0.75; 95% CI=0.4–1.3) or excluding proxy respondents (OR=0.6; 95% CI=0.3–1.2). In the study by Carreon *et al.* (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to Lee *et al.* (2005). Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), the authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (home and garden use: OR=0.98; 95% CI=0.67–1.43; non-farm jobs: OR=0.83; 95% CI=0.39–1.73) (Yiin *et al.*, 2012).

(iii) Stomach and Esophageal Cancers

In a population-based case control study in eastern Nebraska, Lee *et al.* (2004) investigated pesticide use and stomach and esophageal adenocarcinomas. Cancer cases (stomach=170 and esophagus=137) were identified through the state cancer registry, and confirmed by a pathologist. The exposure assessment was based on self-reported pesticide use, with follow-up telephone interview to verify the reported information. There was no association between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI=0.4–1.5) or esophageal cancer (OR=0.7; 95% CI=0.3–1.4).

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Cancer at Multiple Sites					
De Roos *et al*. (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	All cancers RR =1.0 (0.9-1.2)	No association between glyphosate exposure and all cancer including NHL	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)
Site-Specific Cancers: Lung; Oral cavity; Colon; Rectum; Kidney; Bladder; Prostate and Melanoma					
De Roos *et al*. (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	<u>Lung</u> RR= 0.9 (0.6-1.3) <u>Oral Cavity</u> RR=1.0 (0.5-1.8) <u>Colon</u> RR=1.4 (0.8-2.2) <u>Rectum</u> RR=1.3 (0.7-2.3) <u>Pancreas</u> RR=0.7 (0.3-2.0) <u>Kidney</u> RR=1.6 (0.7-3.8) <u>Bladder</u> RR=1.5 (0.7-3.2) <u>Prostate</u> RR=1.1 (0.9-1.3) <u>Melanoma</u> RR=1.6 (0.8-3.0)	No significant association between glyphosate exposure and cancer of the lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate or melanomas	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Breast Cancer					
Engel *et al*. (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 30,454 wives of licensed pesticide applicators with no history of breast cancer at enrollment	Self-report questionnaire	Direct exposure (wives who applied) OR=0.9 (0.7-1.1) (Exposed: 82 cases, 10,016 controls) Indirect exposure (wives whose husbands applied) OR=1.3 (0.8-1.9) (Exposed: 109 cases, 9,304 controls)	No association between glyphosate exposure and breast cancer	Age, race and state of residence (Iowa and North Carolina). Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Pancreatic Cancer					
Andreotti *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; follow-up to 2004 93 cases 82,503 controls	Self-report questionnaire; validated, reliability tested	Ever-use OR=1.1 (0.6, 1.7) (Exposed: 55 cases)	No association between glyphosate exposure and pancreatic cancer	Age, smoke, diabetes, applicator type. Limited to licensed applicators. Potential exposure to multiple pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Prostate Cancer					
Alavanja *et al.* (2003) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; cancer thru 1999 55,332 male applicators	Self-report questionnaire; validated, reliability tested	No quantitative risk estimate reported	No quantitative estimate due to lack of significant exposure-response association with prostate cancer.	Age, family history. Limited to licensed applicators. Potential exposure to multiple pesticides
Band *et al.* (2011) British Columbia, Canada	Case-Control 1983- 1990 1,516 prostate cancer patients 4,994 age-matched controls	Job exposure matrix for agriculture; detailed occupational history; exposure aggregated over all jobs reported. 60 exposed cases	OR=1.36 (0.83-2.25) (Exposed: 25 cases 60 controls)	No association between glyphosate exposure and prostate cancer	Alcohol consumption, cigarette years, education level, pipe smoking years and respondent
Koutros *et al.* (2013) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2003 1,962 incident cases, including 919 aggressive prostate cancers among 54,412 applicators	Self-report questionnaire, validated	OR=0.93 (0.73-1.18)	No association between glyphosate exposure and prostate cancer	Age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Colorectal Cancer					
Lee *et al*. (2007) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-97; follow-up to 2002 56,813 licensed pesticide applicators	Self-report questionnaire	Colon OR=1.0 (0.7-1.5) (Exposed: 151 cases 49 controls) Rectum OR=1.6 (0.9-2.9) (Exposed: 74 cases 18, controls) Colorectal OR=1.2 (0.9-1.6) (Exposed: 225 cases 67 controls)	No significant association between glyphosate exposure and colon, rectum or colorectal cancer	Age, smoking, state, total days use pesticides. Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Cutaneous Melanoma					
Dennis *et al.* (2010) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 150 cases, 24,554 non-cases	AHS self-report questionnaire	No quantitative risk estimate reported	No quantitative estimate due to lack of an association with cutaneous melanoma	Age, sex, tendency to burn, red hair, sun exposure time, BMI at 20 years

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Soft Tissue Sarcoma					
Pahwa *et al*. (2011) Canada	Case-Control 1991-1994 342 cases, 1506 age/resident matched controls	Self-reported use, structured interview/ questionnaire; cumulative exposure (+/-10 days/yr)	OR=0.90 (0.58-1.40)	No association between glyphosate exposure and soft tissue sarcoma	Significant medical history variables and with strata for the variables of age group and province of residence
Total Childhood Cancer					
Flower *et al*. (2004) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control; hybrid prospective/ retrospective 1993-1998 21, 375 children of licensed pesticide applicators In Iowa (n=17,357) North Carolina (n=4018)	Self-report questionnaire; duration and frequency of pesticide use; Female Family questionnaire (child name)	Maternal use OR=0.61 (0.32-1.16) 32 cases Paternal use (prenatal) OR=0.84 (0.35-2.34);	No association was detected between frequency of parental pesticide application of glyphosate and childhood cancer risk.	Potential exposure to other pesticides. Child age in multiple logistic [standardized incidence ratio (SIR)] was unadjusted

Table 2. Summary of Findings: Solid Tumor Cancer Studies

Study	Study Design	Exposure Assessment	Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)	Conclusions	Potential Confounders Considered
Brain Cancer (Glioma)					
Lee *et al.* (2005a) Nebraska	Population based Case-Control study 1988-1993; 251 glioma cases 498 controls	Self-reported questionnaire information, telephone follow-up for unclear responses; men and women assessed separately	Self-Report OR=0.4 (0.1- 1.6) (Exposed: 4 cases 17 controls) Overall OR=1.5 (0.7-3.1) (Exposed: 17 cases 32 controls) Proxy report OR=3.1 (1.2- 8.2) (Exposed:13 cases 15 controls)	Non-significant excess risk for the overall group, but inconsistent for self-report and proxy indicating recall bias	Age, proxy, respond type
Ruder *et al.* (2004) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin, U.S.A.)	Population-based Case-Control 1995-1997 457 glioma cases 648 population controls	Self-report questionnaire, with telephone based follow-up	No quantitative risk estimate reported for glyphosate.	No association with glyphosate exposure and brain cancer	Farm residence, age, use of other pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Carreon *et al*. (2005) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 341 glioma cases, 528 controls	Self-report questionnaire	Proxy respondents OR=0.75 (0.4-1.3) (Exposed: 18 cases 41 Controls) Excluding proxy OR=0.6 (0.3-1.2) (Exposed:10 cases)	No association with glyphosate exposure and brain cancer	Age, education and use of other pesticide
Yin et al. (2012) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 798 glioma cases 1,175 controls	Self-report questionnaire	Home/garden use OR=0.98; 95% CI=0.67 - 1.43; Non-farm jobs: OR=0.83; 95% CI=0.39-1.73)	No significant positive association with glyphosate exposure and brain cancer	Age, sex, education and use of other pesticide

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Esophagus and Stomach Cancer					
Lee *et al.* (2004b) Nebraska, U.S.A.	Population based Case-Control 1988-1993 137 esophageal cases; 170 stomach cases; 502 controls	Self-report pesticide use, telephone structured interview	<u>Esophagus</u> OR=0.7 (0.3-1.4) (Exposed:12 cases 46 controls) <u>Stomach</u> OR=0.8 (0.4-1.5) (Exposed: 12 cases 46 controls)	No association with glyphosate exposure and esophagus or stomach cancer	Age, sex

2. Non-Solid Tumor Cancer Sites

A number of studies evaluating the possible link between pesticide use and lymphohematopoietic cancers such as leukemia, multiple myeloma and NHL are presented in Table 3.

(i) Leukemia

In a population-based case-control study in Iowa and Minnesota, Brown *et al*. (1990) investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR=0.9; 95% CI=0.5–1.6). The study population (578 cases; 340 living and 238 deceased and 1245 controls) was identified from cancers reported to state registry or authorities in 1981–1984, and the pesticide exposure assessment was performed through in-person interviews which the authors state likely reduced the exposure misclassification (*i.e.* incorrect exposure information). Although the large sample size is a strength of this study, the limitations include not controlling for exposure to other pesticides, limited power for studying the effects of glyphosate use, and the potential for recall bias.

In a Swedish population-based case-control study, 121 cases in men and 484 controls matched for age and sex were identified in 1987–1992 through the Swedish cancer registry. The authors reported a non-statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR=3.1; 95% CI=0.8–12.0), controlling for age, sex, and residential location. However, because these results are based on only 4 glyphosate-exposed cases and 5 exposed controls as noted by the authors, this risk should be interpreted with caution. Also, there was limited power to detect an effect and there was no adjustment for other exposures. At this time, there is limited available literature concerning glyphosate use and leukemia (Nordstrom *et al*., 1998).

(ii) Multiple Myeloma

In a follow-up analyses using the same study population from Iowa and Minnesota Brown *et al.* (1993) investigated whether pesticide use is also related to multiple myeloma. Among men in Iowa (173 cases, 605 controls), the authors observed a statistically non-significant elevated association with glyphosate use (OR=1.7; 95% CI=0.8–3.6). However, the authors caution that while the study may lend support to the role of pesticides in general, the study limitations preclude use of the evidence as a definitive finding for any one compound.

De Roos *et al*. (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on a small number (32) of cases. For applicators with the full data set (54,315) and without adjustment for other variables the OR was 1.1; 95% CI=0.5–2.4. In the fully adjusted model, there was a non-statistically significantly elevated risk (OR=2.6; 95% CI=0.7–9.4), however, the number of participants included in this analysis was lower (n=40,716) due to missing data for the covariates. The authors postulated that the increased myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses.

Sorahan (2015), using Poisson regression, re-analyzed the AHS data reported by De Roos *et al.* (2005) to examine the reason for the disparate findings in relation to the use of a full data set versus the restricted data set. Risk ratios were calculated for exposed and non-exposed subjects. When adjusted for age and sex, the OR was 1.12 with the 95% CI of 0.5–2.49 for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of other pesticides did not have any effect (OR=1.24; 95% CI=0.52–2.94).

In a population-based case-control study among men in six Canadian provinces between 1991 and 1994, researchers reported non-statistically significantly elevated odds of multiple myeloma in relation to glyphosate use (OR=1.22; 95% CI=0.77–1.93), based upon 32 glyphosate exposed multiple myeloma case and 133 controls (Pahwa *et al.*, 2012).

Kachuri *et al.* (2013), using the same Canadian study population as above, further explored multiple myeloma in relation to days per year glyphosate used in 342 cases of multiple myeloma and 1357 controls. For ever use, the OR=1.19 and 95% CI=0.76–1.87. For light users (≤2 days/year) there was no association (OR=0.72; 95% CI=0.39–1.32; 15 exposed cases); whereas, for heavy users (>2 days/ year), there was a non-significant increased odds ratio (OR=2.04; 95% CI=0.98–4.23; 12 exposed cases). The limitation in this study was the same as the previous study (*i.e.*, the number of cases and controls exposed to glyphosate were very low).

Landgren *et al.* (2009), within the AHS study population, investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS). The MGUS is considered a pre-clinical marker of multiple myeloma progression. The authors did not observe a link with glyphosate use in the AHS cohort (OR=0.50; 95% CI=0.20–1.0).

(iii) <u>Lymphoma</u>

The National Cancer Institute (NCI) performed a series of population-based case-control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred non-Hodgkin lymphoma (NHL) cases and controls, the identified cases were through disease registries which in many cases, were histopathologically confirmed. The investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time.

Cantor *et al.* (1992), in a case-control study of NHL interviewed a total of 622 white men and 1245 population based-controls in Iowa and Minnesota. Only 26 cases and 49 controls ever handled glyphosate yielding an OR of 1.1 with the 95% CI of 0.7–1.9. The study, however, did not adjust for exposure to other pesticides.

De Roos *et al.* (2003) used pooled analysis (n=3,417) of three case-control studies of NHL conducted in white men in Nebraska, Kansas and in Iowa and Minnesota. Based on 36 exposed cases and 61 exposed controls, the risk estimates for the association between glyphosate exposure and NHL was significant (OR=2.1; 95% CI=1.1–4.0) in the logistic regression analyses. However, utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, there was an increase risk, but the increase was not statistically significant (OR=1.6; 95% CI=0.90–2.8). Overall, the data showed a suggestive association.

Based on the above findings, Lee *et al*., (2004) examined the relationship between asthma and pesticide exposure, and NHL. Pooling data from several midwestern states (IA, MN, and NE) increased the study sample size, and additional pesticide use information was incorporated to adjust the risk estimate (duration and frequency of use, telephone follow-up interview). The study included 872 men with NHL and 2381 frequency-matched controls. The authors reported that the OR associated with glyphosate was not statistically significantly different among those with asthma (OR=1.2; 95% CI=0.4–3.3; 6 exposed cases) and among those without asthma (OR=1.4; 95% CI=0.98–2.1; 53 exposed cases), adjusting for age, state and vital status.

The three studies discussed above (Cantor *et al*., 1992; De Roos *et al*., 2003 and Lee *et al*., 2004) reflect the same population in the AHS and used different levels of information (duration and frequency of exposure) and different analytic techniques [hierarchical regression and stratified analysis (by atopy)]. While studies with increasing levels of refinement to methodology report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

A population-based case–control study (Hardell and Erickson, 1999) investigated the exposure to pesticides as a risk factor for NHL in Sweden during 1987–1990. Exposure data were ascertained by comprehensive questionnaires and supplemented by telephone interviews. Of the 404 cases and 741 controls, only 4 glyphosate-exposed cases and 3 controls were included in the study. In a univariate analysis, the risk estimate was elevated, but precision was low (OR=2.3; 95% CI=0.40–13.0).

Hardell *et al*. (2002) analyzed pooled data from two case-control studies from Sweden that examined NHL (Hardell and Erickson, 1999) and another on hairy cell leukemia, a subtype of NHL (Nordstrom *et al*., 1998). In the univariate analysis glyphosate exposure was found to be significantly increased (OR=3.04; 95% CI=1.08–8.52) but, when study site, and vital status were considered in a multivariate analyses, there was a non-statistically elevated risk among glyphosate users (OR=1.85; 95% CI=0.55–6.20). However, the wide range of the CI suggest that the study is under powered and, therefore the findings do not allow definitive conclusion on the association of NHL and glyphosate exposure.

In another case-control study in Sweden (1999–2003), Eriksson *et al*. (2008) examined the effects of exposure to different agents and NHL among 910 NHL cases and 1016 non-NHL controls. Glyphosate exposure which was reported in 29 cases and 18 controls produced an OR of 2.02 (95% CI=1.10–3.71) in a univariate analysis and an OR of 1.51 (95% CI=0.77–2.94) in a multivariate analysis conducted to clarify the relative importance of exposure to different pesticides. When exposure was for more than 10 days/year, the OR was 2.36 (95% CI=1.16–4.40) and for exposure less than 10 days/year, the OR was 1.69 (95% CI=0.7–4.07). The risk estimate was elevated also for B-cell lymphoma and glyphosate exposure (OR=1.87; 95% CI=0.998–3.51).

McDuffie *et al.* (2001) in a multicenter-population based study among men of six Canadian provinces estimated the association between glyphosate and NHL. The study included 517 cases and 1506 controls identified betwen1991and 1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases, implemented a two-tiered exposure questionnaire; and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the test results. There was a non-statistically significant increased risk of NHL from glyphosate exposure. The OR was 1.26 and the 95% CI was 0.87–1.80 for 51 exposed cases, adjusted for age and province and the OR was 1.20 with a 95% CI of 0.83–1.74 when adjusted for age, province and high-risk exposure (adjusted for statistically significant medical variables such as history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative).

In a follow-up study which controlled for exposure to other pesticides, the risk to NHL from glyphosate exposure was attenuated. Glyphosate exposure which was reported in 19 cases and 78 controls produced an OR of 0.92 with 95% CI of 0.54–1.55 (Hohenadel *et al.*, 2011). Within this series of studies, the authors also evaluated Hodgkin lymphoma (HL), and observed little statistical evidence of an association, using similar study design and methods. Among the 38 cases exposed to glyphosate the OR was 0.99 with a 95% CI of 0.62–1.56 (Karunanayake *et al.,* 2012).

In a hospital-based case control study conducted between 2000 and 2004 in France, authors identified 491 NHL cases and 456 age-and sex-matched controls, and performed telephone-based questionnaire to assess pesticide and other confounding variables. There was no association between NHL and glyphosate use; for the 12 exposed cases, the OR was 1.0 and the 95% CI was 0.5–2.2). For Hodgkin lymphoma, for the 6 exposed cases, the OR was 1.7 and the 95% CI was 0.6–5.0 (Orsi *et al*., 2009).

The EPILYMPH case-control study was conducted across six countries in Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain) to explore the role of occupational exposure to specific chemicals and risk of lymphoma overall, B-cell lymphoma and other subtypes. Although the study recruited 2348 cases and 2462 controls, only a very small number of cases were exposed to glyphosate (n=4) and controls (n=2). A non-significant increase in OR was observed for B-cell lymphoma (OR=3.1; 95% CI=0.6–17.1), but the estimate is unstable due to the small number of exposed cases and controls (Cocco *et al.,* 2013)

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL using data from six of the above mentioned studies (McDuffie *et al*., 2001; Hardell *et al*., 2002; DeRoos *et al*., 2003 and 2005; Eriksson *et al*., 2008; and Orsi *et al*., 2009). Since the authors identified a variety of sources of heterogeneity between publications, they calculated meta-risk ratio (RR) estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. They reported I^2 values, which represented the percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. For glyphosate, the meta-risk ratio was 1.5 with a 95% CI of 1.0–2.0 and the I^2 value was 32.7% indicating greater inconsistency in these data sets. This study combined multiple smaller studies that on their own were very limited in statistical power to detect differences.

The 2015 IARC evaluation noted that fully adjusted risk estimates in two of the Swedish studies (Hardell *et al.*, 2002 and Eriksson *et al.*, 2008) were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, IARC conducted a reexamination of the results of these studies. For an association between glyphosate exposure and NHL, the IARC estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65), I^2=0%; p=0.589 for heterogeneity) (IARC 2015).

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Leukemia					
Brown *et al*. (1990) Iowa and Minnesota, U.S.A.	Population-based Case-Control 1981-1984 578 cases 1245 controls	In person interview; surrogates used.	OR=0.9 (0.5-1.6) (Exposed:15 cases 49 controls)	No association between glyphosate exposure and leukemia	Vital status (alive, dead), residency (IA or MN), tobacco use, parent, sibling, or child with a lymphopoietic cancer, high risk occupation and exposure to substances (benzene, hair dyes etc) related to risk of leukemia
Nordstrom *et al*. (1998) Sweden	Population-based Case-Control 1987-1992 121 cases 484 controls	Self-reported pesticide questionnaire and follow-up telephone interview	OR=3.1 (0.8-12) (Exposed: 4 cases 5 controls)	A non-statistically significant elevated risk of hairy cell leukemia	Age, sex, country of residence (selected using matching, dissolved matching analyses) No adjustment for exposure from other pesticides
Multiple Myeloma					
Brown *et al*. (1993) Iowa, U.S.A.	Population based Case-Control 1981-1984 173cases 650 controls	Interview based questionnaire with follow-up	OR=1.7 (0.8-3.6) (Exposed: 11 cases 40 controls)	Limited power to assess association of glyphosate exposure and multiple myeloma	Age and vital status

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
De Roos *et al*. (2005) Iowa and North Carolina, U.S.A.	Prospective Cohort 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	Full data set RR =1.1 (0.5-2.4) (Exposed: 32 cases) Adjusted for age etc RR=2.6 (0.7-9.4)	No risk for full data set. Excess risk only with no missing information of 22 cases in the restricted data set (Sorahan, 2015)	Missing data on covariates when multiple adjustments were made, limiting interpretation
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=2.4 (0.8-7.3) (Exposed: 5 cases 18 controls)	No significant association with glyphosate exposure and multiple myeloma	Age, center, socioeconomic category
Pahwa *et al*. (2012) Canada	Population based Case-Control 1991-1994 342 cases 1506 controls	Self-reported pesticide use, structured interview with questionnaire; cumulative exposure (+/-10 days/yr)	OR=1.22 (0.77-1.93) (Exposed: 32 cases 133 controls)	No significant association with glyphosate exposure and multiple myeloma	Significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Kachuri *et al.* (2013) Canadian Provinces	Population based Case-Control 1991-1994 342 cases 1357 controls	Self-administered questionnaire	For ever use OR=1.19 (0.76-1.87) Exposed: 32 cases 121controls Light (<2 d/yr) use OR=0.72 (0.39 -1.32) Exposed: 15 cases 88 controls Heavy (>2 d/yr) use OR=2.04 (0.98-4.23) Exposed: 12 cases 29 controls	No association with glyphosate exposure and multiple myeloma for ever or light users Increase for heavy users is non-significant	Relatively low response rate
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
Landgren *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 678 participants	Self-administered questionnaire	OR=0.5 (0.2-1.0)	No association with glyphosate exposure and MGUS, a premalignant disorder that often precedes multiple myeloma	Age and education

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Non-Hodgkin Lymphoma (NHL)					
Cantor *et al.* (1992) Iowa and Minnesota, U.S.A.	Population based Case-Control 1980-1983 622 cases 1245 controls	Structured interview, questionnaire response; farm activities and specific pesticide use	OR=1.1 (0.7-1.9) Exposed: 26 cases 49 controls	No association with glyphosate exposure and NHL	Vital status, age, state, smoking, family history, high risk occupation, high risk exposure. Not controlled for exposure to other pesticides.
De Roos *et al.* (2003) Iowa, Nebraska, Minnesota, Kansas, U.S.A.	Case-Control 1983-1986\Nebraska 1979-1981\Kansas 1979-1986 870 white male cases 2569 white male controls	Interview-based questionnaire, demographic	Logistic regression OR=2.1 (1.1-4.0) Exposed: 36 cases 61 controls Hierarchical regression OR=1.6; (0.9-2.8)	Significant increased OR in logistic model but in the hierarchical model, the OR attenuated and no significant association with glyphosate exposure and NHL	Age, study site, use of all other pesticides (group); hierarchal regression informed priors based on chemical-specific information
Lee *et al.* (2004a) Iowa, Nebraska, Minnesota, U.S.A	Population based Case-Control 1980-1986 872 white male cases	In person, structured interview (pesticide use, duration, frequency, first and last year used); 5-yr follow-up interview, 10-min telephone on pesticide use	Non-asthmatic OR=1.4 (0.98-2.1) (Exposed: 53 cases 91 controls) Asthmatic OR=1.2 (0.4-3.3) (Exposed: 6 cases 12 controls)	No significant association with glyphosate exposure and NHL either for asthmatics or non-asthmatics	Adjusted for age, vital status, state

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	OR=1.1 (0.7-1.9 (Exposed: 92 cases)	No significant association with glyphosate exposure and NHL	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education
Hardell and Erickson (1999) Sweden	Population based Case-Control 1987-1990 404 male cases 741 male controls	Questionnaire and follow-up interview	<u>Univariate</u> OR=2.3 (0.4-13.0) (Exposed: 4 cases 3 controls) <u>Multivariate</u> OR=5.8 (0.6-54)	Some evidence of a link with glyphosate, matching variables; cannot conclude regarding causal role for any specific pesticide	Age, region, vital status (matching). Few subjects exposed. Variables used in multivariate were no specified. Study has limited power to detect an effect
Hardell *et al.* (2002) Sweden	Population based Case-Control Combined Hardell 1999 with another case-control study examining hairy cell leukemia (one of 61 types of NHL) 1987-1990 515 cases 1141 controls	Questionnaire and follow-up interview	<u>Univariate</u> OR=3.04 (1.08-8.52) (Exposed: 8 cases 8 controls) <u>Multivariate</u> OR=1.85 (0.55-6.20)	Risk attenuates when adjusted for other variables in the multivariate analysis	Age, country, study site, vital status, other pesticide exposure in the multivariate analysis

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Eriksson *et al*. (2008) Sweden	Population based Case-Control 1999-2002 910 cases 1016 controls	Questionnaire and follow-up interview	Univariate OR=2.02 (1.10-3.71) (Exposed: 29 cases 18 controls) Multivariate OR=1.55 (0.77-2.94) With <10 days/ year OR=1.69 (0.7-4.07) (Exposed: 12 cases 9 controls) With > 10 days/year OR=2.36 (1.04-5.37) (Exposed: 17 cases 9 controls) B-cell lymphoma OR=1.87 (0.998-3.51)	Suggestive association for NHL with glyphosate exposure	Age, sex, year of diagnosis. Multivariate analysis adjusted for exposure to other pesticides
McDuffie *et al*. (2001) Canada	Population based Case-Control 1991-1994 517 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	Univariate OR=1.26 (0.87-1.8) (Exposed: 51 cases 133 controls) Multivariate OR=1.20 (0.83-1.74)	No significant association with glyphosate exposure and NHL	Adjusted for statistically significantly medical variables (history of measles, mumps, cancer, allergy shots, and a positive family history of cancer) males only

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Hohenadel *et al.* (2011) Canada	Case-Control 1991-1994 513 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	OR=0.92 (0.54-1.55) (Exposed: 19 cases 78 controls)	No significant association with glyphosate exposure and NHL	Age, province and proxy respondent, males only
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.0 (0.5-2.2) (Exposed: 12 cases 24 controls)	No association with glyphosate exposure and NHL	Age, center, socioeconomic category
Cocco *et al.* (2013) Czech Republic, France, Germany, Italy, Ireland and Spain	EPICLYMPH Case-Control 1998–2003 2348 cases 2462 controls	Occupational exposure; trained interviewers conducted in person interviews with cases and controls	OR=3.1 (0.6-17.1) (Exposed: 4 cases 2 controls)	No significant association with glyphosate exposure and B-cell	Age, center, socioeconomic category
Hodgkin Lymphoma					
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.7 (0.6-5.0) (Exposed: 6 cases 15 controls)	No significant association with glyphosate exposure and HL	Age, center, socioeconomic category

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Karunanayake *et al.*, (2012). Canada	Case-Control 1991-1994 361 cases 1,506 controls	Questionnaire and follow-up interview	<u>Univariate</u> OR=1.14(0.74-1.76) (Exposed :38 133 controls) <u>Multivariate</u> OR=0.99 (0.62-1.56)	No association with glyphosate exposure and HL	History of measles, acne, hay fever, shingles and positive family history of cancer in a first-degree relative

D. Discussion

In epidemiologic studies, the quality of the exposure assessment is a major concern since the validity of the evaluations depends in large part on the ability to correctly quantify and classify an individual's exposure. During their life-time, farmers are typically exposed to multiple pesticides and several of them are used together posing a challenge for identifying specific risk factors. Moreover, there is no direct information on pesticide exposure or absorbed dose because analyses are based on self-reported pesticide use. The studies included in this epidemiology assessment relied primarily on questionnaires and interviews to describe participants' past and/or current exposure to glyphosate. Since the questionnaires are commonly used to account for exposure and capture self-reporting, it can be subject to misclassification and recall bias. For example, case-control studies are at risk of recall bias in the reporting of pesticide use in the past because cases may have spent more time thinking about past exposures than controls. This could lead to differential misclassification and bias relative risk from null. The possible effect of confounding factors, which are related to both the exposure of interest and the risk of disease, may make it difficult to interpret the results. Therefore, the ability of epidemiologic studies to provide convincing evidence of causation under such circumstances may be limited. Causation is suspected if several studies are consistent in their findings and; if the association between the agent and the risk of disease is strong (*i.e.*, high risk ratio). Support from animal data will help to make the case for causation, particularly by establishing biological plausibility and the existence of a potential mechanism. Another important consideration in assessing epidemiologic studies is that commercially formulated products (not the active ingredient) are used by farmers. For example, glyphosate is sold as Roundup®, which is a combination of the active ingredient and other chemicals that often include a surfactant (polyethyleneamine) used to enhance the spreading of spray droplets when they contact the foliage. Thus, it is possible that different glyphosate-containing formulations were used across the different studies.

Most of the studies discussed here were hypothesis-generating in nature, consisted of small sample sizes with limited power to detect associations and evaluated use of glyphosate in addition to several other pesticides and often evaluated risk of multiple different types of cancer. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis, limit epidemiologic inference. This hypothesis-generating evidence observed in the studies requires further prospective follow-up studies to determine whether a true association with glyphosate is indeed null. The case-control studies are retrospective studies and are susceptible to recall bias for exposure reporting which could account for discrepancies in the study findings. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could also explain these inconsistencies in the data. In contrast, a prospective cohort study evaluates a number of diseases simultaneously and facilitates performance of periodic assessments of agricultural and other exposures. Periodic assessment of recent exposures enhances recall and reduces non-differential misclassification. The ability to determine exposure prior to the onset of a disease eliminates the case-recall bias, which was an issue identified as a weakness in case-control studies.

IV. EVALUATION OF CARCINOGENICITY IN ANIMALS

A total of 11 chronic toxicity/carcinogenicity studies (7 rat and 4 mouse) were included in this weight of evidence review. Of these, six studies were submitted for review to EPA under the registration/reregistration programs including two studies in rats (MRID No. 496311701 and 49704601) and one in mouse (MRID No. 49631702) not previously reviewed. Data for review of the other five studies were obtained from a published review article by Greim *et al.*, 2015 and were available online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423. The IARC acknowledged the Greim *et al.,* (2015) review article, but did not evaluate the studies cited in the review because the information provided in the review and its supplement was insufficient.

For this assessment, each study reported in the Greim *et al.,* (2015) review article was evaluated in accordance with the agency's 2012 Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf). In accordance with this guidance, the following four studies were not included in this weight of evidence assessment since there is low confidence were determined to be unreliable for carcinogenicity evaluation.

- A two year feeding study in Sprague-Dawley rats (Excel, 1997) was not included due to the lack of test article characterization (no purity of test material).

- The two-year drinking water study in Wistar rats reported by Chruscielska *et al*., (2000) was not included since the tested material was a formulated product (13.6% ammonium salt) and there were a number of deficiencies (lack of purity, water consumption and body weight data) in the conduct and reporting of the study.

- An initiation-promotion study (George *et al.*, 2010) in male Swiss mice that tested a commercial formulation of glyphosate (41%) with study deficiencies (*e.g.* small number (20) of animals, tested only males, and lack of histopathological examination).

- A carcinogenicity study in Swiss mice (Feinchemie Schwebda, 2001) was not included due to the presence of viral infection within the colony, which confounded the interpretation of the study findings. Malignant lymphomas were reported in this study in all groups. However, lymphomas are one of the most common types of spontaneous neoplastic lesions in aging mice (Brayton *et al.*, 2012). Murine leukemia viruses (MuLVs) are a common cause of lymphoma in many different strains of mice (Ward 2006). Tadesse-Heath *et al.* (2000) reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice. Although the incidences in this study were within or near the normal variation of background occurrence, it is not clear whether or not the viral component may have contributed to incidence value reported or the lower survival seen at the high dose in the study. Raw data are not available to perform appropriate statistical analyses of the lymphomas correcting for the intercurrent mortality.

A. Carcinogenicity Studies in Rats

1. Lankas, G, P. A Lifetime Study of Glyphosate in Rats. December 23, 1981. Unpublished report No. 77-2062 prepared by Bio Dynamics, Inc. EPA Accession. No. 247617 – 247621. MRID No. 00093879.

a. Experimental Design

Groups of Sprague-Dawley rats (50/sex/dose) were fed diets containing glyphosate (98.7%, pure) at concentrations of 0, 30, 100 or 300 ppm for 26 months. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in females were maintained.

b. Survival Analysis

There were no treatment-related effects on survival at any dose level.

c. Discussion of Tumor Data

There was an increase in the incidences of interstitial cell tumors in the testes of male rats at the low (3/5; 6%), mid (1/50; 2%) and the high dose (6/50; 12%; P=0.013 pairwise comparison) when compared to controls (0/50; 0%). In 1991, HED's Cancer Peer Review Committee (CPRC) did not consider the increases to be treatment-related based on the following weight of evidence considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5%; range, 3.4% to 6.7%) and 5) no interstitial cell tumors were seen when tested at much higher doses in the same strain of rats in an another study (discussed below). The CARC agreed with the CPRC conclusion and rationale and noted additional rat studies which also showed no effect on interstitial cell tumors.

Although there was no evidence of a treatment-related increase in the incidences of pancreatic islet cell tumors in male rats, the data are presented in Table 4 since this tumor also seen in the second study discussed below.

Table 4. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats (MRID 00093879)				
Tumor Type	0 ppm	30 ppm	100 ppm	300 ppm
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Combined (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

d. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

The CPRC concluded that the highest dose tested was not adequate to assess the carcinogenic potential of glyphosate. Consequently, a second study was conducted (discussed below).

2. Stout, L. D. and Rueckerf, P.A. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; September, 26, 1990, MRID No. 41643801; Historical Controls; MRID No. 41728701.

a. Experimental Design

Groups of Sprague-Dawley rats (60/sex/dose) were fed diets containing glyphosate (96.5%, pure) at dietary concentrations of 0, 2000, 8000 or 20,000 ppm 24 months. These levels were equivalent to 0, 89, 362 or 940 mg/kg/day, respectively, for the males and 0, 113, 457 or 1183 mg/kg/day, respectively, for the females. An interim sacrifice was conducted on 10 rats/sex/dose at 12 months.

b. Discussion of Tumor Data

The most frequently seen tumors were pancreatic cell adenomas, hepatocellular adenomas and thyroid C-cell adenomas in males. Data for these tumors and the respective historical control data are presented in Tables 5 thru 11.

Pancreatic cell adenomas are presented in Table 5 and the historical control data are presented in Table 6. Hepatocellular adenomas seen in males are presented in Table 7 and the historical control data are presented in Table 8. The thyroid C-cell adenomas and/or carcinomas observed in males and females are presented in Tables 9 and 10, respectively, and the historical control data are presented in Table 11.

(i) Pancreas

There was no statistically significant trend test by dose for pancreatic islet cell tumors. Increased incidences of adenomas only were observed at the low- and high-dose groups but not at the mid-dose group.

Table 5. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	1/43[a] (2) 0.170	8/45 (18) 0.018*	5/49 (10) 0.135	7/48[b] (15) 0.042*
Carcinomas (%) P=	1/43[c] (2) 0.159	0/45 (0) 0.409	0/49 (0) 0.467	0/48 (0) 0.472
Combined (%) P=	2/43 (2) 0.241	8/45 (18) 0.052	5/49 (10) 0.275	7/48 (15) 0.108

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 81 in the 20,000 ppm group
c. First carcinoma observed at week 105 in the controls (0 ppm)
* Significant in a pair-wise comparison ($P<0.05$)

Historical control data on the incidence of pancreatic islet cell adenomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 6.

Table 6. Historical Control Data — Pancreatic Islet Cell Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)							
Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Tumor Incidence	2/68	5/59	4/69	1/57	5/60	3/60	3/59
%	2.9%	8.5%	5.8%	1.8%	8.3%	5.0%	5.1%

The CPRC concluded that the pancreatic islet cell adenomas are not treatment-related based on the following weight of evidence considerations: 1) although the incidences at the low (18%) and high (15%) dose groups exceeded the historical control range (1.8–8.5%), there was lack of statistical significance in Cochran-Armitage trend test; 2) the tumor incidence in the concurrent control was at the low end of the historical control range; 3) considerable inter-group variability in the numbers of males with tumors (*i.e.*, no dose-response); 4) there were no preneoplastic changes; 5) there was no progression from adenomas to carcinomas; and 6) the apparent statistical significance of the pairwise comparisons of the treated groups with the concurrent control may be due to the low incidences in the controls and not to an actual carcinogenic response. Furthermore, the incidences of pancreatic cell tumors for the two studies did not show dose-response and the incidences were within the historical control range (0 to 17%) reported in the open literature (Arnold *et al.,* 1985; Borelli *et al.*, 1990; Borzelleca *et al.*, 1986, 1989, 1990; Burnett *et al.*, 1988; Trochimowicz *et al.*, 1988). The CARC agreed with the CPRC conclusion and rationale and noted subsequent rat studies which also showed no effect on islet cell tumors.

(ii) Liver

There was a dose trend for adenomas only. There were no statistically significant increases in the occurrence of benign or malignant hepatocellular tumor types (Table 7). The observed variations in incidence were within the range of the historical control data.

Table 7. Glyphosate: Hepatocellular Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/44[a] (5) 0.016*	2/45 (4) 0.683	3/49 (6) 0.551	7/48[b] (15) 0.101
Carcinomas (%) P =	3/44 (7) 0.324	2/45 (4) 0.489	1/49 (2) 0.269	2/48[c] (4) 0.458
Adenoma/Carcinoma (%) P =	5/44 (11) 0.073	4/45 (9) 0.486	4/49 (8) 0.431	9/48 (19) 0.245

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 88 in the 20000 ppm group
c. First carcinoma observed at week 85 in the 20000 ppm group

Historical control data on the incidence of hepatocellular adenomas and carcinomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 8.

Table 8. Historical Control Data : Hepatocellular Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)							
Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Adenomas	5/60 (8.3%)	11/68 16.2%)	1/70 (1.4%)	3/59 (5.1%)	11/60 (18.3%)	5/60 8.3%)	4/60 (6.7%)
Carcinomas	4/60 (6.7%)	0/68 (0%)	1/70 (1.4%)	2/59 (3.4%)	3/60 (5%)	1/60 (1.7%)	0/60 (0%)

The CPRC concluded that the slightly increased incidence of adenomas in male rats are not treatment-related since: 1) the increase was not statistically significant in pairwise comparison with the controls; 2) the incidences were within the historical control range; 3) except for a single animal at the mid-dose late in the study (89 weeks), no hyperplasia, preneoplastic foci or other non-neoplastic lesions were seen; and 4) there was no evidence of progression from adenomas to carcinomas. The CARC agreed with the CPRC conclusion and rationale.

(iii) Thyroid

The increased incidences in C-cell adenomas observed at the mid and high-dose groups of rats of both sexes did not show a statistically significant difference in pairwise comparisons with the controls (Table 9 and 10, respectively). There was a dose trend observed for adenomas and adenomas/carcinomas in females (P=0.03). Historical control data are presented in Table 11.

Table 9. Glyphosate: Thyroid C-Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/54[a, b] (4) 0.069	4/55 (7) 0.348	8/58 (14) 0.060	7/58 (12) 0.099
Carcinomas (%) p =	0/54 (0) 0.452	2/55[c] (4) 0.252	0/58 (0) 1.000	1/58 (4) 0.518
Adenoma/Carcinoma (%) p =	2/54 (11) 0.077	6/55 (11) 0.141	8/58 (14) 0.060	8/58 (14) 0.060

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 54 in the controls
c. First carcinoma observed at week 93 in the 20,000 ppm

Table 10. Glyphosate: Thyroid C-Cell Tumors in Female Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P=	2/57[a] (4) 0.031*	2/60 (7) 0.671	6/59[b] (10) 0.147	6/55 (11) 0.124
Carcinomas (%) P=	0/57 (0) 0.445	0/60 (0) 1.000	1/59[c] (2) 0.509	0/55 (0) 1.000
Adenoma/Carcinoma (%) p=	2/57 (4) 0.033*	2/60 (3) 0.671	7/59 (12) 0.090	6/55 (11) 0.124

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 72 in the controls
c. First carcinoma observed at week 93 in the 8000 ppm group.

Table 11. Historical Control Data – Thyroid C-cell Tumors in Sprague-Dawley Rats (MRID No. 41728701)		
Tumor Type	Males	Females
Adenomas	1.8 – 10.6%	3.3 – 10.0%
Carcinomas	0.0 – 5.2%	0.0 – 2.9%

The CPRC concluded that the thyroid tumors in either sex are not treatment-related since: 1) the increased incidences exhibited no statistically significant trend or pairwise comparisons with the controls in males; 2) in females, there was a trend but no pairwise significance; 3) there was no progression from adenomas to carcinomas; and 4) there was no dose-related increase in severity of grade or incidence of hyperplasia in males or females. The CARC agreed with the CPRC conclusion and rationale and noted other rat studies which showed no effect on thyroid C-cell tumors.

c. Non-Neoplastic Lesions

There were no treatment-related precursor lesions at any dose level.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was near or beyond the limit dose (1000 mg/kg/day).

3. Atkinson, C., Strutt, A., Henderson, W., et al. (1993). 104-Week chronic feeding/ oncogenicity study in rats with 52-week interim kill. Inveresk Research International (IRI), Tranent, Scotland. Study No. 438623; IRI Report No. 7867. April 7, 1993. MRID No. 49631701. Unpublished.

a. Experimental Design

In a combined chronic toxicity/carcinogenicity study, glyphosate (98.9% pure) was administered to 50 male and female Sprague-Dawley rats/sex/dose in the diet at 0, 10, 100, 300, and 1000 mg/kg/day for 104 weeks. An interim sacrifice was conducted on 15 rats/sex/dose after 52 weeks of treatment.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

There were no treatment-related increases in the occurrence of any tumor type in this study.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was the limit dose (1000 mg/kg/day) and at this dose increased salivary gland weight accompanied by cellular alterations in the mandibular and/or parotid glands occurred in both males and females.

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4. Brammer. (2001). Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK: Syngenta. (MRID No. 49704601).

a. Experimental Design

In a combined chronic toxicity study, glyphosate acid (97.6% pure) was administered to groups of Wistar rats in the diet. Groups of 52 male and 52 female rats received diets containing 0, 2,000, 6,000, and 20,000 ppm glyphosate for 24 months. The achieved doses were 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437 or 1498 mg/kg/day in females, respectively. Three satellite groups of 12 rats/sex/group were also included for interim sacrifice at 12 months of treatment. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

As shown in Table 12, there was an increase in the incidence of hepatocellular adenomas in male rats at the high dose when compared to controls. This increase was not considered to be treatment-related due to 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the range (0–11.5%) of historical controls for this strain (Wistar) of rats in 26 studies conducted during the relevant time period (1984–2003) at the testing laboratory; and 5) the 0% incidence in concurrent controls is lower than the average background incidence for liver adenomas in male Wistar rats.

Table 12. Liver Adenomas in Male Wistar Rats
Fisher's Exact Test and Exact Trend Test Results

	0	2000	6000	20000
Adenomas (%) P =	0/52[a] (0) 0.00804**	2/52 (4) 0.24757	0/52 (0) 1.00000	5/52 (10) 0.02826*

a =Number of tumor-bearing animals/Number of animals examined.

In addition, statistically higher survival (P=0.02) was observed in males at 20,000 ppm at the end of 104 weeks relative to controls, and an overall trend for improved survival was observed in treated males (P=0.03). The inter-current (early) deaths were 37/52, 36/52, 35/52, and 26/52 for the control, low, mid and high dose groups, respectively. The terminal deaths were 16/52, 17/52, 18/52, and 26/52 for the control, low, mid and high dose groups, respectively. This survival bias in the high dose group could easily explain a modestly higher incidence of an age-related background tumor like liver adenoma (and fits with lack of associated lesions). In the 1990 study in Sprague-Dawley rats (MRID No. 41643801) there was also a weak but significant trend test for liver adenomas in males (P=0.02, no pairwise); however, in that study adenomas in all treatment groups were still within the historical control and the CPRC concluded that this effect was not treatment-related, as discussed above. The lack of increased liver tumor incidence in the other rat studies provide additional evidence for lack of an actual carcinogenic response in the liver.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in any organs of either sex at any dose level tested.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes (1214 mg/kg/day in males and 1498 mg/kg/day in females) exceeded the limit dose (1000 mg/kg/day). Treatment-related findings at these doses were observed in the liver and kidney, notably renal papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, hematuria and slight increases in the incidence of proliferative cholangitis and hepatitis.

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5. Feinchemie Schwebda. (1996). Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats. Bangalore, India: Rallis India, Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (96.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 100, 1000, and 10000 ppm glyphosate for 24 months. The average achieved doses were 0, 7.4, 73.9, and 740.6 mg/kg/day. Parameters evaluated included clinical signs, body weights, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy, and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no non-neoplastic lesions at any dose level in either sex.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The doses tested were determined to be adequate in both sexes since the highest dose tested (741 mg/kg/day) approached the limit dose (1000 mg/kg/day).

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6. Arysta Life Sciences. (1997a). HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (94.6–97.6% pure) was administered to groups of Sprague-Dawley rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 3000, 10000, or 30000 ppm glyphosate for 24 months. The achieved doses were 0, 104, 354 or 1127 mg/kg/day in males and 0, 115, 393, or 1247 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose 10,000 ppm (1127 mg/kg/day in males and 1247 mg/kg/day in females) exceed the limit dose (1000 mg/kg/day) and there were increased cecum weights, distension of the cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, and decreased body weights.

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7. Nufarm. (2009a). Glyphosate Technical: Dietary Combined Chronic Toxicity/ Carcinogenicity in the Rat. Shardlow, Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic toxicity study, glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group received diets containing 0, 1500, 5000, and 15,000 ppm glyphosate for 24 months. To ensure that a received limit dose of 1000 mg/kg/day was achieved, the highest dose level was progressively increased to 24000 ppm. The achieved doses were 0, 86, 285 or 1077 mg/kg/day in males and 0, 105, 349 or 1382 mg/kg/day, in females. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in either sex at any dose level.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest doses 1077 mg/kg/day in males and 1382 mg/kg/day in females exceed the limit dose (1000 mg/kg/day).

B. Carcinogenicity Studies in Mice

1. Knezevich, A.L and Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamic Inc., dated July 21, 1983. Report No. 77-2011. EPA Accession No. 251007 – 251009, and 251014.

a. Experimental Design

In a carcinogenicity study, groups of 50 male and female CD-1 mice received glyphosate (99.78%, pure) at dietary levels of 0, 1000, 5000, or 30,000 ppm for two years. These doses were equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, and histopathological examination.

b. Discussion of Tumor Data

The incidences of renal tubule adenomas were as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose; and 3/50 at the high dose (TXR No. 0004370).

In 1985, the Registrant directed a re-evaluation of the original renal section by a consulting pathologist (Dr. Marvin Kuschner). This evaluation identified a small renal tubule adenoma in one control male mouse (animal number 1028) which was not diagnosed as such in the original pathology report (TXR No. 0004855).

In 1986, at the request of the agency, additional renal sections (3 sections/kidney/mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate-treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice were not compound-related (TXR No. 0005590).

At the request of the agency, the Pathology Work Group (PWG) examined all sections of the kidneys including the additional renal sections. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 13. The PWG noted that because differentiation between tubular-cell adenoma and tubular-cell carcinoma is not always clearly apparent and because both lesions are derived from the same cell type, it appropriate to combine the incidences for purposes of evaluation of statistical analysis. Statistical analyses are presented in Table 14. The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the controls and there was no evidence of a significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound-related nephrotoxic lesions, including pre-neoplastic changes, were not present in male mice in this study (TXR No. 0005590).

Table 13. Glyphosate: Kidney Tumor in Male CD-1 Mice — PWG				
Dose/Tumor Type	Control	1000 ppm	5000 ppm	30,000 ppm
	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Tubular-cell adenoma	1/49	0/50	0/50	1/50
Tubular-cell carcinoma	0	0/50	1/50	2/50
Combined incidence	1/49 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)

Statistical analysis of the male mouse renal tumors diagnosed by the PWG are presented below in Table 14.

Table 14. Kidney Tumors in Male CD-1 Mice — PWG Cochran-Armitage Trend & Fisher's Exact Test (MRID 00130406)				
Tumor Type	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Adenomas (%) P =	1/49 (2) 0.4422	0/49 (0) 1.0000	0/50 (0) 1.00000	1/45 (2) 0.7576
Carcinomas (%) P =	0/49 (0) 0.0635	0/49 (0) 1.0000	1/50 (2) 0.5051	2/50 (4) 0.2525
Combined (%) P =	1/49 (2) 0.0648	0/49 (0) 1.0000	1/50 (2) 0.7576	3/50 (6) 0.3163

Historical control data from the testing laboratory (Bio-dynamics) during the glyphosate-study period (1976-1982) are presented in Table 15.

Table 15. Historical Control Data- Kidney tumors in CD-1 Mice — Bi/dynamics Inc.														
Study I.D	A		B		C		D		E		F		G	
Study Period	6/78 - 7/80		12/77-4/80		12/77-3/80		10/78-4/81		11/78-4/81		11/77-4/80		10/77-4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma		1	0	0	0	0	0	0	0	2	0	0	0	0

Historical control data from 14 studies conducted between 1977 and 1981 at the testing laboratory indicated that the mouse renal tumors ranged from 0 to 3.3% and the incidence in the current study (3/50; 6%) exceeded the upper limit of the historical control range (TXR No. 0007252).

The CPRC determined that glyphosate produced an equivocal carcinogenic response in male mice characterized by an increased incidence of renal tubular neoplasms. The biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls for adenomas, carcinomas and the combined tumors; b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (*e.g.* tubular necrosis/regeneration, hyperplasia, hypertrophy, etc.), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males; e) although the incidences exceeded the historical control, this finding did not override the lack of statistical significance of comparison to the concurrent controls. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not consider the renal tumors to be treatment-related. The CARC reaffirmed the CPRC conclusion and rationale. Also, the lack of increased renal tumors in the other mouse studies in the same strain provides additional evidence for lack of an actual carcinogenic response in the kidneys.

c. Non-Neoplastic Lesions

The incidence of centrilobular hepatocyte hypertrophy was slightly but not significantly increased in high-dose male mice at terminal sacrifice if all mice were included in the analyses. Centrilobular hepatocyte necrosis was significantly ($P \leq 0.01$) increased in high-dose male mice (10/50; 20%) compared to controls (2/49; 4%). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice. There was a dose-dependent increase in the proximal tubular epithelial basophilia in female mice; the incidences were: 0/50 (0%) in the controls, 2/50 (4%) at the low dose, 4/50 (8%) at the mid dose, and 9/50 (18%) at the high dose ($P \leq 0.01$). All other tissue alterations occurred sporadically and were found with approximately equal frequency and severity in contro1 and treated animals. These were considered unrelated to glyphosate treatment.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The high dose tested in males (4945 mg/kg/day) and females (6069 mg/kg/day) was approximately 4 to 6-fold higher than the limit dose (1000 mg/kg/day), which produced highly significant reduction in body weights in both sexes. Therefore, the doses tested were determined to be adequate to assess the carcinogenic potential of glyphosate in this study.

2. **Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993). Glyphosate: 104 week dietary carcinogenicity study in mice. Inveresk Research International, Tranent, EH33 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702.**

a. Experimental Design

In a carcinogenicity study, glyphosate (97.5 – 100.2% pure) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. No interim sacrifices were performed. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, necropsy and histopathological examination.

b. Discussion of Tumor Data

As shown in Table 16, hemangiosarcomas were found in 4/45 (9%) high-dose male mice compared to none in the controls. In the treated mice at the high dose, one had the tumors present in the liver and spleen, one had the tumor present in the liver only, one had the tumors present in the liver, spleen, and prostate, and one had the tumor present in the spleen only. No hemangiosarcomas were found in the control or low- and mid-dose mice.

Table 16. Hemangiosarcomas in Male CD-1 Mice Fisher's Exact Test and Exact Trend Test Results				
Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcomas (%) P =	0/47[a] (0) 0.00296**	0/46 (0) 1.00000	0/50 (0) 1.00000	4/45 (9) 0.05332

a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in hemangiosarcomas in male mice was not considered to be treatment-related due to 1) tumors seen only at the limit dose; 2) absence of statistical significance in the pairwise analysis; 3) the incidences was near or the same as the upper limit (0–8%) for the performing laboratory; 4) hemangiosarcomas were not seen in male mice in the other three studies when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4348–5874 mg/kg/day) in this strain of mouse; 6) the considerable inter-group variability in the number of female mice with this tumor (0, 2 , 0 and 1 in the control, low-, mid- and high-dose groups, respectively); 7) Hemangiosarcomas are commonly observed in mice as both spontaneous and treatment-related tumors arising from endothelial cells; 8) hemangiosarcomas appear in both sexes but are generally more common in males (CD-1); 9) As vascular tumors, they can occur at different sites but liver and spleen tend to be the most common sites in male mice.

c. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose tested was the limit dose (1000 mg/kg/day).

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3. Arysta Life Sciences. (1997b). HR-001: 18-Month Oncogenicity Study in Mice. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.,* 2015).

a. Experimental Design

In a carcinogenicity study, groups of ICR-CD-1 mice (50/sex/group received diets containing glyphosate (94.6–97.6% pure) at 0, 1600, 8000 or 40,000 ppm for 18 months. The achieved doses were 0, 165, 838 or 4348 mg/kg/day in males and 0, 153, 787 or 4116 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes exceeded (4-fold) the limit dose (1000 mg/kg/day).

~~4.~~ Nufarm. (2009b). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In another feeding study, CD-1 mice (50/sex/dose) received glyphosate (94.6–97.6%, pure) at 0, 500, 1500, or 5000 ppm for 18 months. The calculated test substance intake was 0, 85, 267 or 946 mg/kg/day. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, gross necropsy and histopathological examination.

b. Discussion of Tumor Data

In male mice at the high dose (5000 ppm) there were increases in the incidences of adenocarcinomas of the lung and malignant lymphomas as shown in Tables 17. For the lung adenocarcinomas, the increases did not reach statistically significant pairwise differences, although the trend was significant. For the malignant lymphomas there was a trend and pairwise significance. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

Table 17. Lung Adenocarcinomas and Malignant Lymphomas in Male CD-1 Mice (Greim *et al.*, 2015)
Fisher's Exact Test and Exact Trend Test Results

Dose (ppm)	0	500	1500	5000
Lung Adenocarcinoma (%) P =	5/51[a] (10) 0.02906**	5/51 (10) 0.62953	7/51 (14) 0.37996	11/51 (22) 0.08609
Malignant Lymphoma (%) P =	0/51 (0) 0.006633**	1/51 (2) 0.50000	2/51 (4) 0.24752	5/51 (10) 0.02820*

a= Number of tumor bearing animals/Number of animals examined.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in lung adenocarcinomas was not considered to be treatment-related due to: 1) absence of statistical significance in the pairwise analysis; 2) the incidences in all treatment groups including the controls were within the historical control range (1.43–26%) for the performing laboratory; and 3) lung tumors were not seen in the other three studies when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

Historical control data and results from the 5 studies can be used to put this finding into perspective. The malignant lymphomas were not considered to be treatment-related since the 0% incidence of this lesion in the concurrent control for male mice was lower than the historical control mean (4.5%) and range (1.5–21.7%) in this strain and age of mice (Gikins and Clifford, 2005; Son and Gopinath, 2004). Therefore, the apparent statistical significance of the pairwise comparisons of the high dose male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response. In addition, malignant lymphomas were not seen in the other three studies in this strain of mice when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

c. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose (947 mg/kg/day) tested approached the limit dose (1000 mg/kg/day).

IV. TOXICOLOGY

A. Metabolism

Single or repeated doses of radiolabeled ^{14}C-glyphosate were administered orally to male and female Sprague-Dawley rats. Following a single oral dose of, ^{14}C-glyphosate, 30 to 36% of the dose was absorbed and less than 0.27% of the dose was eliminated as CO_2. 97.5% of the administered dose was excreted in the urine and feces as the parent compound, glyphosate. Amino methyl phosphonic acid (AMPA) was the only metabolite found in urine (0.2–0.3% of the administered dose) and feces (0.2–0.4% of the administered dose). Less than 1.0% of the absorbed dose remained in tissues and organs, primarily in bone tissue. Repeated dosing at 10 mg/kg did not significantly change the metabolism, distribution or excretion of glyphosate.

In a second study, male and female Sprague-Dawley rats received single intraperitoneal injections of radiolabeled ^{14}C-glyphosate at 1150 mg/kg. Blood samples were collected 0.25, 0.50, 1, 2, 4, 6 and 10 hours after injection. Femoral bone marrow samples were collected from one third of the male and female rats sacrificed at 0.5, 4, or 10 hours after injection. Thirty minutes after injection of glyphosate, the concentration of radioactivity in the bone marrow of male and female rats was equivalent to 0.0044% and 0.0072%, respectively, of the administered dose. Assuming first order kinetics, the decrease in radioactivity in bone marrow occurred with a half-life of 7.6 and 4.2 hours for males and females, respectively. Similarly, the half-lives of the radioactivity in plasma were approximately 1 hour for both sexes. These findings indicate that very little glyphosate reaches bone marrow, that it is rapidly eliminated from bone marrow, and that it is even more rapidly eliminated from plasma.

B. Mutagenicity

In 1991, the Carcinogenicity Peer Review Committee concluded that there was no evidence of genotoxicity for glyphosate based on negative findings in submitted guideline studies for the bacterial reverse mutation test (MRID 00078620), *in vitro* mammalian cell gene mutation test in CHO cells (MRID 00132681), *in vivo* mammalian bone marrow chromosomal aberration test (MRID 00132683) and a "rec assay" used to detect DNA-damaging agents in *Bacillus subtilis* (MRID 00078619) (TXR 0008898).

Glyphosate has also been evaluated for its genotoxic potential in other regulatory and published literature studies. Extensive reviews of the available genotoxicity studies for glyphosate and glyphosate products were conducted by Williams *et al.* (2000) and by Kier and Kirkland (2013). IARC also conducted a review of the publically available genetic toxicity data for glyphosate and glyphosate-based formulations (IARC, 2015).

Williams *et al.*, (2000) concluded that "glyphosate is neither mutagenic nor clastogenic." Similarly, Kier and Kirkland (2013) concluded a "lack of genotoxic potential for both glyphosate and glyphosate based formulations (GBFs) in core gene mutation and chromosomal effect endpoints." Kier and Kirkland (2013) also stated that "the observations of DNA-damage effects seems likely to be secondary to cytotoxic effects." However, IARC (2015) concluded that "there is strong evidence that glyphosate causes genotoxicity." It should be noted that the IARC's conclusion was based not only on studies conducted with the active ingredient but also on studies conducted with the formulation products such as Roundup. Roundup is a combination of the active ingredient and other chemicals, including a surfactant (polyoxyethyleneamine) which enhances the spreading of spray droplets when contact foliage. Of note, the review article by Kier and Kirkland (2013) and supplemental information provided on the publisher's website were not considered in the IARC evaluation.

In this assessment, the CARC considered a total of 54 studies including those submitted to the agency under 40 CFR Part 158 as well as the studies presented in the review articles by Williams *et al.* (2000), Kier and Kirkland (2013), and the IARC monograph (2015). Consistent with OPP's Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf), literature studies discussed in the reviews such as IARC that did not meet the Klimisch criteria for reliability (*e.g.* lack of adequate glyphosate purity information for the test material) were not considered by the CARC. The CARC determined the mutagenic potential of glyphosate in humans by conducting a weight-of-evidence evaluation of the results from the cited bacterial reversion (Ames) assays, *in vitro* mammalian gene mutation assays, *in vitro* and *in vivo* chromosomal aberration and micronucleus assays as well as other relevant assays evaluating DNA damage.

1. Bacterial reverse mutation assays

As shown in Table 18, glyphosate was not mutagenic in any of the *in vitro* bacterial mutation assays using *S. typhimurium* or *E. coli* tester strains with or without microsomal S9 metabolic activation. These results are consistent with the negative findings in the previously reviewed EPA guideline (870.5100) bacterial reverse gene mutation study (MRID 00078620).

Table 18. Results from Bacterial Reverse Gene Mutation Assays[1]

Author	Cell/Strain[2]	Purity	Highest test concentration	Results –S9	Results +S9
Akanuma,M. (1995)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.7%[3]	5000 µg/plate	Negative	Negative
Callander, R.D. (1996)	TA98, TA100, TA1535, TA1537; WP2P and WP2*uvr*A	95.6%[3]	5000 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	76.1%[4]	100 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	96.4%	3160 µg/plate	Negative	Negative
Flügge, C. (2009)	TA98, TA100, TA102, TA1535, TA1537	98.8%	3160 µg/plate	Negative	Negative
Jensen, J.C. (1991)	TA98, TA100, TA1535, TA1537	98.6%	2500 µg /plate w/o S9; 5000 µg /plate w/ S9	Negative	Negative
Li and Long (1988)	TA98, TA100, TA1535, TA1537, TA1538;	98%	5000 µg/plate	Negative	Negative
NTP (1992)	TA97, TA100, TA1535	98%	10,000 µg /plate	Negative	Negative
Schreib, G. (2010)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96%	5000 µg/plate	Negative	Negative
Shirasu et al. (1978)	TA98, TA100, TA1535, TA1537, TA1538 and WP2*uvr*A	98.4%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007c)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.0%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007a)	TA98, TA100, TA1535, TA1537; WP2uvrA	95.1%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009b)	TA98, TA100, TA1535, TA1537;WP2P and WP2*uvr*A	96.3%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009a)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96.66%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007b)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	97.7%	5000 µg/plate	Negative	Negative
Suresh, T.P. (1993)	TA98, TA100, TA1535, TA1537, TA1538	96.0%	1000 µg/plate	Negative	Negative
Thompson, P.W. (1996)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.3%	5000 µg/plate	Negative	Negative

1. Studies cited in Williams *et al*. (2000), Kier and Kirkland (2013), or IARC monograph.
2. *S. typhimurium* strains (TA97, TA98, TA100, TA102, TA1535, TA1537, and/or TA1538) or *E. coli* strains (WP2P and WP2*uvr*A)
3. Glyphosate acid
4. Monoammonium glyphosate salt

2. *In vitro* mammalian cell gene mutation assays

Glyphosate did not induce forward mutations in mouse lymphomas cells or Chinese hamster ovary (CHO) cells in the presence or absence of metabolic (S9) activation (Table 19).

Table 19. Results from mammalian gene mutation assays[1].

Author	Assay Type	Cell type	Purity	Highest conc.	Result -S9	Result +S9
Clay (1996)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	95.6%	1.0 mg/mL	Negative	Negative
Jensen, J.C. (1991)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	98.6%	5.0 mg/mL	Negative	Negative
Li and Long (1988)	*In vitro* mammalian gene mutation	CHO cells/ HGPRT locus	98%	22.5 mg/mL	Negative	Negative

1. Studies cited in Williams's *et al*. (2000), Kier and Kirkland (2013), or IARC monograph.

3. *In vitro* chromosomal aberration assays

Lioi *et al.* (1998a, 1998b) reported positive findings for chromosomal aberrations in human and bovine lymphocytes treated with glyphosate *in vitro* in the absence of S9 activity. As discussed in the Williams review, there is less confidence in the Lioi *et al.* results based on the use of an unusual 72-hour treatment protocol and the observation of reduced cell growth in glyphosate-exposed cells (an indication of a toxic effect) which can affect the evaluation of the study. Lioi *et al.* also reported chromosomal damage in lymphocytes treated with other known non-genotoxic pesticides in this study at concentration ranges similar to where they reported effects for glyphosate. By contrast, when the tests were performed according to the OECD guideline, Van de Waart (1995) reported no significant increase in chromosomal aberrations in human lymphocytes treated with up to 0.56 mg/mL (-S9) and 0.33 mg/mL (+S9) glyphosate, which are concentrations 3 orders of magnitude higher than those at which Lioi *et al.* reported aberrations. Glyphosate was negative in two other *in vitro* chromosomal aberrations studies using human lymphocytes (Fox, 1998; Manas *et al.* 2009) and did not induce chromosomal aberrations in Chinese hamster lung cells (Matsumoto, 1995; Wright, 1996). A summary of the findings is presented in Table 20.

Table 20. Results from *in vitro* chromosomal aberration assays[1].						
Authors	**Assay**	**Cell type**	**Purity**	**Highest test concentration**	**Result -S9**	**Result +S9**
Van de Waart (1995)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	0.56 mg/mL with S9; 0.33 mg/mL w/o S9	Negative	Negative
Fox, V. (1998)	Chromosome Aberration	Human peripheral lymphocytes	95.6%[2]	1250 ug/mL	Negative	Negative
Lioi et al. (1998a)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	1.4 mg/L	Positive	Not Tested
Manas et al. (2009)	Chromosomal Aberration	Human peripheral lymphocytes	96%	6 mM	Negative	Not Tested
Lioi et al. (1998b)	Chromosomal Aberration	Bovine peripheral lymphocytes	>98%	2.9 mg/L	Positive	Not Tested
Matsumoto, K. (1995)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.68%[2]	1000 ug/mL	Negative	Negative
Wright, N.P. (1996)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.3%	1250 ug/mL	Negative	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

4. ***In vivo* micronucleus and chromosomal aberration assays**

Numerous studies were evaluated to determine the potential for glyphosate to induce micronuclei in rodent bone marrow cells. Studies included both intraperitoneal (IP) and oral routes of glyphosate administration. In a literature study by Bolognesi *et al.* (1997), the authors reported an induction of micronuclei in male mice treated with up to 300 mg/kg (injected as two ½ doses). It is noted that this study included only 3 animals/dose, rather than the 5 animals/dose recommended in the agency's test guideline (870.5395). In another literature study, Manas *et al.* (2009) reported an induction of micronuclei in BALB/C mice when tested up to 200 mg/kg glyphosate. However, there is some concern regarding how the micronuclei were scored in this study. As stated in the Kier and Kirkland review, Manas *et al.* (2009) reported their findings as an increase in micronucleated erythrocytes rather than polychromatic erythrocytes. Scoring all erythrocytes rather than immature polychromatic erythrocytes can impact the interpretation of the study as the effects cannot be solely attributed to treatment by the test article. Suresh *et al.* (1993) reported an increase in micronuclei in females only in Swiss albino mice treated with 5 mg/kg glyphosate; however, this occurred at a dose that is more than twice the limit dose for the agency's guideline study. Although the above authors reported positive findings, a vast majority of the *in vivo* genotoxicity studies (including the previously reviewed guideline mammalian bone marrow chromosomal aberration test) were negative at doses similar to or higher than the studies discussed above, regardless of the dosing regimen or route of administration. Furthermore, glyphosate was also negative in two rodent dominant lethal tests. A summary of the findings are reported in Table 21.

Table 21. Results from *in vivo* genotoxicity assays[1].

Author	Assay Type	Species/strain	Purity	Highest conc.	Results	Comments
Bolognesi *et al.* (1997)	Micronucleus test	Male mice (strain not provided)	99.9%	300 mg/kg	Positive	Two IP injections of ½ dose; 3 mice/dose
Durward, R. (2006)	Micronucleus test	Young adult male and female albino Crl:CD-1TM(ICR)BR mice	95.7%	600 mg/kg	Negative	Single IP injection; Significant increase in % PCEs per 1000 erythrocytes was observed in the 24-hour; however not 48-hour at 600 mg/kg
Flügge, C. (2009)	Micronucleus test	Male and female CD rats	98.8%	2000 mg/kg	Negative	Single dose; oral gavage
Fox and Mackay (1996)	Micronucleus test	Male and female CD-1 BR mice	95.6%[2]	5000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2005)	Micronucleus test	Male and female NMRI mice	97.73%	2000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2008)	Micronucleus test	NMRI male mice	99.1%	2000 mg/kg	Negative	Single dose; oral gavage
Jensen, J.C. (1991)	Micronucleus test	Young adult male and female NMRI SPF mice	98.6%	5000 mg/kg	Negative	Single dose; oral gavage
Manas *et al.* (2009)	Micronucleus	BALB/C mice	96%	200 mg/kg	Positive	Two IP doses, 1 day apart
NTP (1992)	Micronucleus test	Male and female B6C3F1 mice	99%	11,379 mg/kg/day	Negative	Dietary admin., 13 weeks
Suresh, T.P. (1993)	Micronucleus test	Young Swiss albino male and female mice	98.6%	5000 mg/kg	Males: Negative Females: Positive	Two doses 1 day apart; oral gavage
Suresh, T.P. (1994)	Mouse Bone Marrow Chromosome Aberration	Male and female Swiss albino mice	96.8%	5000 mg/kg	Negative	Two doses, 24 hours apart; oral gavage
Suresh, T.P. (1992)	Rodent dominant lethal test	Male and female Wistar rats	96.8%	500 mg/kg (single dose); 100 mg/kg (5 daily doses)	Negative	
Wrenn (1980)	Rodent dominant lethal test	Mouse; gavage	98.7%	2000 mg/kg	Negative	

1. Studies cited in Williams *et al*., (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid
3. IP= intraperitoneal injection

5. Other genotoxicity assays

Inconsistent responses were reported in a number of assays designed to detect DNA damage, including sister chromatid exchange (SCE) assay, unscheduled DNA synthesis assay, and the comet assay (also known as the single cell electrophoresis assay). Positive responses in these assays do not necessarily indicate a chemical is DNA-reactive (*i.e.* mutagenic), but rather that DNA damage occurred under conditions of the assay. Glyphosate was also negative in two Rec-DNA repair tests in *B. subtilis*. The results of these genotoxicity studies are presented in Table 22.

Table 22. Additional genotoxicity assays of glyphosate

Authors	Assay Type	Cell Type	Purity	Highest test conc.	Results
Bolognesi *et al.* (1997)	Sister chromatid exchange (SCE)	Human peripheral blood (*in vitro*)	99.9%	1000 ug/mL	Positive
Lioi *et al.* (1998a)	SCE	Human peripheral blood (*in vitro*)	>98%	1.4 mg/L	Equivocal
Lioi *et al.* (1998b)	SCE	Bovine peripheral blood (*in vitro*)	>98%	2.9 mg/L	Equivocal
Li and Long (1988)	Unscheduled DNA synthesis (UDS)	Rat hepatocytes (*in vitro* exposure)	98%	0.125 mg/mL	Negative
Rossberger,(1994)	UDS	Primary rat hepatocytes	98%	111.69 mM	Negative
Bolognesi *et al.* (1997)	DNA Damage /reactivity/UDS	Mouse; IP administration	99.9%	300 mg/kg	Equivocal
Bolognesi *et al.* (1997)	DNA Damage/reactivity/UDS	Mouse; IP; alkaline solution of extracted DNA	99.9%	300 mg/kg	Positive
Alvarez-Moya et al. (2014)	Comet assay	Human lymphocytes	96%[2]	700 µM	Positive
Lueken *et al.* (2004)	Comet assay	Human fibroblasts GM 5757	98.4%	75 mM	Negative
Manas *et al.*(2009)	Comet assay	Liver Hep-2 cells	96%	7.5 mM	Positive
Mladinic et al. (2009)	Comet assay	Human lymphocytes	98%	580 ug/mL (toxic); approximately 3.43 mM	Positive
Rossberger, S. (1994)	DNA repair test	Male SD rat primary hepatocytes	>98%	111.69 mM	Negative
Akanuma, M. (1995)	DNA repair test (Rec- assay)	*Bacillus subtilis* M45 rec-/ H17 rec+	95.68%[2]	240 ug/disk	Negative
Li and Long (1988)	DNA repair test (Rec assay)	*B. subtilis* H17, rec+; M45, rec-	98%	2 mg/disk	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

6. Conclusions

In summary, glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronuclei or chromosomal aberration studies considered in this assessment by the CARC. Some positive results were reported in SCE and comet assays in the open literature; however, there is no convincing evidence that the DNA damage is a direct effect of glyphosate exposure, but rather may be secondary to cytotoxicity or oxidative damage.

C. Structure-Activity Relationship

At present there are no structurally related pesticides registered by the agency which resemble glyphosate. Sulfosate, the trimethylsulfonium salt of glyphosate (also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl) glycine anion (PMG) and the trimethylsulfonium cation (TMS). Sulfosate was evaluated for its carcinogenic potential following dietary administration to male and female mice at 0, 10, 1000 or 8000 ppm (equivalent to 0, 16, 159 or 1341 mg/kg/day, respectively) for 18 months, and in male and female Sprague-Dawley rats at 0, 100, 500, or 1000 ppm (equivalent to 0, 5.4, 27 or 557 mg/kg/day, respectively) for two years. There was no evidence of carcinogenicity in either species. Sulfosate is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans" based on the absence of carcinogenicity in mice and rats in two acceptable studies. Based on the available mutagenicity studies, there is no concern for mutagenicity (TXR Nos. 0006452 and 0011156).

D. Subchronic and Chronic Toxicity Studies

1. Subchronic Toxicity

In a 90-day feeding study (MRID No. 00036803) CD-1 mice were fed diets containing 0, 250, 500 or 2500 mg/kg/day of glyphosate for three months. Body weight gains of the high-dose males and females were about 24% and 18% lower, respectively, than those of the controls. Body weight gains of the low-dose and mid-dose groups were comparable to those of the controls. For systemic toxicity, the NOAEL is 500 mg/kg/day and the LOAEL is 2500 mg/kg/day, based on decreased body weight gain in both sexes.

In a 90-day feeding study (MRID No. 40559401), Sprague-Dawley rats were fed diets containing 0, 63, 317, and 1267 mg/kg/day of glyphosate, respectively in males and 0, 84, 404 and 1623 mg/kg/day of glyphosate, respectively, in females. Treatment-related findings were: (1) increased serum phosphorus and potassium in all treated groups, males and females; (2) increased serum glucose in the mid-dose and high-dose males; (3) increased blood urea nitrogen (BUN) and serum alkaline phosphatase in the high-dose males; and (4) occurrence of pancreatic lesions in the high-dose males (pancreas was not examined at the low-dose and mid-dose groups). Based on these findings, the systemic NOAEL is <1000 ppm (not determined definitively) for both sexes.

2. Chronic Toxicity

(i) Rats

A chronic feeding/carcinogenicity study (MRID No. 00093879) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 30, 100, or 300 ppm of glyphosate for 26 months. These levels were equivalent to 0, 3, 10, and 34 mg of glyphosate/kg/day, respectively. There were no effects based on any of the parameters examined (toxic signs, mortality, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights and organ/tissue pathology). Therefore, the NOAEL for systemic toxicity is 300 ppm (males: 31 mg/kg/day and females: 34 mg/kg/day).

A second chronic feeding/carcinogenicity study (MRID No. 41643801) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 2000, 8000, or 20,000 ppm of glyphosate for two years. These levels were equivalent to 0, 89, 362, or 940 mg/kg/day, respectively, for the males and 0, 113, 457, or 1183 mg/kg/day, respectively, for the females. Treatment-related effects observed only in the high-dose group included: (1) decreased body weight gain in females; and (2) increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight, and increased liver weight/brain weight ratio (relative liver weight) in males. No significant systemic effects were observed in the low-dose and mid-dose male and female groups. Therefore, the NOAEL for systemic toxicity is 8000 ppm (males: 362 mg/kg/day and females: 457 mg/kg/day) and the LOAEL is 20,000.

In a combined chronic toxicity/carcinogenicity study (MRID No. 49631701), glyphosate (98.9% a.i.) was administered to 85 Sprague-Dawley rats/sex/dose in the diet for 104 weeks ater 0, 10, 100, 300, and 1000 mg/kg/day to both sexes over the course on the study. Designated for the toxicity portion of the study were 35 rats/sex/dose with the remainder designated for the oncogenicity portion of the study. There were no statistical differences between treated and control groups in survival rates. Pale feces were observed during weeks 16–104 in both sexes at the high dose and in females from the low-mid and high-mid dose levels. No treatment-related effect was observed in food consumption, hematology, ophthalmology, and gross pathology data. Males from the high-dose group had statistically lower mean body weight ($P \leq 0.01$) by 5% to 11% beginning Week 2 of the study until Week 104, and at termination was 10% lower (-14% weight gain). Females at the high dose had statistically lower body weight ($P \leq 0.05$) by 5% to 12% beginning Week 20 through Week 80 (with several exceptions), and at termination was 8% lower (-11% weight gain). Statistically increased ALP activities (+46% to +72%) were observed in males at the high dose throughout the study except for the 51 week interval when the mean value was 31% higher than control. Elevated ALP activities were observed in females at the high dose (+34% to +53%) throughout the study, and through most of the study at the high-mid dose by +20% to +67%, though not always statistically significant. Urinalysis data showed reduced pH (5.5–6) in males at the high dose throughout the study.

The absolute liver weight was decreased significantly in females at the high dose after 52 weeks, but after correcting for final body weight the difference was statistically significant at the three highest doses. The parotid salivary gland weight was increased significantly in males at the three highest doses (56–111%) after 52 weeks, but not after 104 weeks. The combined weight of the sublingual and submaxillary salivary glands was significantly increased by 13% (22% after correcting for body weight) at the high dose after 52 weeks. In females, the parotid gland was not affected but the sublingual and submaxillary combined weight was significantly higher by about 15%. The changes in salivary gland weights were accompanied by increased incidence of mild to severe parotid salivary gland cell alterations and slight to moderate mandibular salivary gland cell alterations were observed in both sexes at the 52-week and 104-week intervals. The lesions were described as cells and/or acini that appeared larger and stained in a weakly basophilic manner without showing a tendency toward proliferative or degenerative changes over time. In males, the increased incidence and severity of lesions in the parotid gland were significant ($P \leq 0.01$) at 100, 300, and 1000 mg/kg bw/day at 52 weeks, and significant at 300 and 1000 mg/kg bw/day at 104 weeks. The increased incidence of lesions in the mandibular gland were significant at 300 and 1000 mg/kg bw/day at 52 weeks and significant ($P \leq 0.001$) at 100, 300, and 1000 mg/kg bw/day at 104 weeks. In females, the increased incidence of parotid lesions was significant at 300 and 1000 mg/kg bw/day at 52 weeks, and significant at 100, 300, and 1000 mg/kg bw/day at 104 weeks. The increased incidence in the mandibular gland lesions was significant at the high dose at both 52 and 104 weeks. The incidence and/or severity of kidney nephropathy decreased in males at 100, 300, and 1000 mg/kg bw/day at 52 weeks and at the high dose at 104 weeks. Urothelial hyperplasia significantly decreased in females from the high dose group at both the 52-week and 104-week intervals. The LOAEL in male and female Sprague-Dawley rats administered glyphosate for 104 weeks in the diet was 100 mg/kg bw/day based on microscopic lesions in the parotid and mandibular salivary glands. The NOAEL was 10 mg/kg bw/day (MRID No. 49631701).

In another chronic toxicity/carcinogenicity study (MRID No. 49704601), groups of 52 male and 52 female Alpk:APSD (Wistar-derived) rats were fed diets containing glyphosate at 0, 2000, 6000, or 20,000 ppm for two years. These doses were equivalent to 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437, or 1498 mg/kg/day in females, respectively. Treatment-related findings were confined to the liver and kidneys at the highest dose (20,000 ppm). In both sexes, treatment-related changes manifested as papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria. The LOAEL was 20,000 ppm (1214 mg/kg/day in males and 1498 mg/kg/day in females) and the NOAEL was 6000 ppm (361 mg/kg/day in males and 437 mg/kg/day in females)

(ii) <u>Mice</u>

In a carcinogenicity study (MRID No. 00251007), glyphosate (Technical, 99.7% a.i.) was administered to groups of 50 male and 50 female CD-1 mice/sex/dose in the diet at dose levels of 0, 1000, 5000, or 30,000 ppm (approximately equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Cage-side and detailed clinical observations were done. Body weight and food intake were monitored throughout the study. Water consumption was measured during months 12 and 24. Erythrocyte, as well as total white cell counts and differentials, were done at months 12, 18, and 24. Tissues and organs were collected from all mice whether dying during the study or at terminal sacrifice. Microscopic analyses were done on all collected tissues.

No treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weight of high-dose males was significantly decreased 9% while the absolute liver weight of high-dose males was significantly decreased 16%; however, no significant treatment-related effects were found on the liver-to-body-weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17. Neither were statistically significant, and no microscopic histological correlates were found. The incidences of centrilobular hepatocyte hypertrophy were slightly, but not significantly increased in high-dose male mice. Centrilobular hepatocyte necrosis was significantly higher in high-dose males (10/50** (20%) vs. control 2/49 (4%), P≤0.01). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice; however, proximal tubular epithelial basophilia was significantly increased in high-dose females (9/50 (18%) vs control 0/50 (0%), P≤0.01). No other microscopic treatment-related effects were found. Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 835 mg/kg bw/day for males and 968 mg/kg bw/day for females) (MRID No. 00251007).

In another carcinogenicity study (MRID No. 49631702), glyphosate (97.5–100.2% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. Mortality, body weight, body weight gain, and food consumption were monitored throughout the study. WBC differential counts were done during Weeks 52, 77, and 102 of the study. Organ weights were measured and tissues collected for microscopic analyses. Treatment of male and female mice for 104 weeks did not increase mortality and did not decrease body weight, body weight gain or food consumption. No treatment-related clinical signs of toxicity were observed and no effects were found on WBC differential counts. Treatment did increase the absolute and relative thymus weights of male and female mice treated with 300 or 1000 mg/kg bw/day approximately 2–3-fold, but only the results of male mice were statistically increased. However, no treatment-related effects were found microscopically. At necropsy, the incidence of lung masses was slightly increased in high-dose male mice, but were considered coincidental. Microscopically, there was a slight, but statistically significant increase in mineral deposition in the brains of mid- and high-dose male mice. A non-significant increase was observed in female mice. Kidney cysts were also slightly but statistically increased in low- and mid-dose males, but no increase of cortical tubular eosinophilic droplets was found in female mice. The significance of these findings is questionable since they did not follow a dose-response. The systemic NOAEL for glyphosate in male and female CD-1 mice treated up to 104 weeks was 1000 mg/kg bw/day. A LOAEL was not identified (MRID No. 49631702).

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

A. Evidence for Carcinogenicity in Humans

The CARC evaluated one cohort study and seven nested case-control studies based on the cohort study population and twenty-five case-control studies that examined the association between glyphosate exposure and one or more cancer outcomes.

1. Cancer at Multiple Sites

Several case-control studies reported no association for cancer of the oral cavity, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, breast or melanoma from exposure to glyphosate (De Roos *et al*., 2005; Engle *et al*., 2005; Lee *et al*., 2007; Andreotti *et al*., 2009; and Dennis *et al*., 2010).

In single case-control studies, no associations were found for cancers of the esophagus, stomach, prostate or soft-tissue sarcoma from exposure to glyphosate (Alavanja *et al*., 2003; Lee *et al.*, 2004; Band *et al.*, 2011; Pahwa, *et al*., 2011; Koutros *et al.,* 2013). No association for childhood cancer was found from maternal or paternal exposure to glyphosate (Flower *et al*., 2004).

2. Brain Cancer

A case-control study in Nebraska and the Upper Midwest Health case-control study in Iowa, Michigan, Minnesota and Wisconsin did not find any no association of glyphosate with adult brain cancer, specifically for gliomas (Ruder *et al*., 2004; Carreon *et al*., 2005; and Lee *et al*., 2005).

3. Leukemia

No significant association with leukemia was reported in a case-control study in Iowa and Minnesota (Brown *et al*., 1990) or in the AHS cohort (De Roos *et al*., 2005). A Swedish case-control study reported a non-statistically significant elevated risk for hairy cell leukemia. However, the authors stipulated that this risk should be interpreted with caution since it was based on only 4 glyphosate-exposed cases (Nordstrom *et al*., 1998).

4. Multiple Myeloma

No significant association for multiple myeloma from exposure to glyphosate was found in three separate population-based case-control studies: one in Iowa and Minnesota (Brown *et al*., 1993) and the other in Iowa and North Carolina, USA (De Roos *et al*., 2005; Sorhan 2015); and the third study in Canada (Pahwa *et al*., 2012; Kachuri *et al*., 2013), and in a hospital-based case-control study in France (Orsi *et al*., 2009). A cohort study found no association with glyphosate exposure and monoclonal gammopathy of undetermined significance, a pre-clinical marker of multiple myeloma progression (Landgren *et al*., 2009).

5. Non-Hodgkin Lymphoma

There is conflicting evidence for an association between glyphosate exposure and NHL; seven case-control studies reported no association in the U.S, Canada, and France, while two case-control studies from Sweden reported positive association.

No association between glyphosate exposure and NHL was found in four population-based case-control studies in the United States: in Iowa and Minnesota (Cantor *et al.*, 1992); in Iowa, Nebraska and Minnesota (Lee *et al.*, 2004a); in Iowa, Nebraska, Minnesota and Kansas (De Roos *et al.*, 2003) and in the AHS cohort with 57,311 licensed pesticide applicators in Iowa and North Carolina (De Roos *et al.*, 2005).

Similarly, no association between glyphosate exposure and NHL was seen in two population-based case-control studies conducted in various Canadian provinces (McDuffie *et al.*, 2001; Hohenadel *et al.,* 2011).

A hospital based case-control study from France did not find an association between glyphosate exposure and NHL (Orsi *et al.*, 2009).

The first report of an association between glyphosate exposure and NHL was in a population-based case-control study from Sweden (OR=23.3; 95% CI=0.40–13.0); however, this finding was based on only 4 glyphosate-exposed cases and 3 controls (Hardell and Erickson, 1999).

In a 2002 follow-up study, data from two case-control studies in Sweden, one on NHL and the other on hairy cell leukemia, were pooled and analyzed. A univariate analysis showed an increased risk (OR=3.04; 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, risk declined (OR=1.85; 95% CI=0.55–6.20) (Hardell *et al.*, 2002).

In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analyses showed a statistically significantly increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51) (Erickson *et al.*, 2008).

A meta-analysis of the six studies (De Roos *et al.,* 2003; 2005; McDuffie *et al.*, 2001; Hardell *et al.*, 2002; Erickson *et al.*, 2008; and Orsi *et al.*, 2009) that showed an association between glyphosate exposure and NHL, resulted in a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014).

In an attempt to address the noted power/sample size issues and after considering the adjusted estimates of the two Swedish studies, IARC performed a meta-analysis of the data and estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65) (IARC, 2015).

In summary, the epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and non-solid tumors: leukemia, multiple myeloma or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate exposure and NHL. Multiple case-control studies and one prospective cohort study found no association with NHL; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data. The CARC recognizes the meta-analysis conducted by IARC to try to address the power/sample size issues. However, given the limitations of the studies used, a different weighting scheme could easily change the meta-risk ratio. Thus, while the epidemiologic literature to date does not support causal association, the CARC recommends that the literature continue to be monitored for studies related to glyphosate and risk of NHL.

B. Evidence for Carcinogenicity in Experimental Animals

1. Evidence for Carcinogenicity in Rats

A total of seven chronic toxicity/carcinogenicity studies in Wistar or Sprague-Dawley strain rats were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 3.0 mg/kg/day to 1500 mg/kg/day for 2-years.

(i) Testes

In Sprague-Dawley rats (MRID No. 00093879), there was a non-dose-related increase in the incidences of interstitial cell tumors in the testes of males at 3 mg/kg/day (6%), 10 mg/kg/day (2%) and 30 mg/kg/day (12%; P=0.013) when compared to controls (0%). The CARC reaffirmed the previous conclusion that these tumors are not treatment related based on the following considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5; range, 3.4% to 6.7%;) and 5) this finding is not replicated in the other studies in the same strain of rats (*i.e.*, no interstitial cell tumors were seen when tested up to 1100 mg/kg/day). The CARC concluded that the interstitial cell tumors are not treatment-related.

(ii) Pancreas

Benign pancreatic islet cell tumors were seen in male Sprague-Dawley rats in two studies. In the first study (MRID No. 00093879), there was no dose response or statistical significance; the incidences for adenomas were: 0%, 10%, 4% and 4% at the control, low, mid, and high dose groups. Carcinomas were seen in one rat at the high dose. In the second study (MRID No. 41643801), there was a statistically significant increase in adenomas at the lowest (100 mg/kg/day) and the highest (1000 mg/kg/day) doses compared to controls: lowest dose, 8/45 (18%; P=0.018); intermediate dose, 5/49 (10%); and highest dose, 7/48 (15%; P=0.042) versus controls, 1/43 (2%). The CARC reaffirmed the previous conclusion that the benign pancreatic islet cell tumors are not treatment-related due to lack of dose-response, absence of pre-neoplastic lesions, lack of progression to malignancy, and incidences within the historical control range (0–17%) reported for this tumor in this strain of rats. This neoplasm was not seen in the other five studies. The CARC concluded that the pancreatic islet tumors are not treatment-related.

(iii) Liver

In male Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of hepatocellular adenomas (P=0.016). The CARC concluded that the minimal increase in adenomas is not treatment-related due lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions, no progression to malignancy, and the incidences were within the historical control range (1.4–18.3%) of the testing laboratory.

In male Wistar rats (MRID No. 49704601), there was a statistically significant trend (P=0.00804) and pairwise significance for the increase in hepatocellular adenomas at the highest (1214 mg/kg/day) dose compared to controls: lowest dose, 2/52 (4%); intermediate dose, 0/52 (0%); and highest dose, 5/52 (10%; P=0.02826) versus controls, 0/52 (0%). The CARC concluded that this increase is not attributable to treatment based on the following considerations: 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the historical control range (0–11.5%).

The CARC noted that survival was better at the high dose (25/52; 13%) compared to the controls (16/52; 8.3%) which could be reason for the slightly higher incidence (5/52) of age-related background tumors like liver adenomas in the absence of any associated lesions. Furthermore, with a weak genotoxic effect one would expect to see an effect on carcinomas (or at least adenomas/ carcinomas, combined) and shorter latency period, which were not observed in this study. With a weak cytotoxic or mitogenic effect one would expect to see an increase in foci and other non-neoplastic lesions. In addition, as discussed above, only a linear trend (no pairwise) was seen for this tumor type in another strain (Sprague-Dawley) for rats where the incidences were still within the historical control range. Also, liver tumors were not seen in the other four studies. This provides additional evidence for lack of an actual carcinogenic response in the liver. The CARC concluded that the liver tumors are not treatment-related.

(iv) Thyroid

In Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of thyroid C-cell tumors in females (P=0.031). The CARC concluded that the minimal increase is not treatment-related due to lack of statistical significance in pairwise comparison, no progression to carcinomas, no increase in severity of grade or incidence of hyperplasia, and the incidences were within the historical control range (3.3–10%). The CARC concluded that the thyroid tumors in female rats are not treatment-related.

In summary, dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female Sprague-Dawley or Wistar rats.

2. Evidence for Carcinogenicity in Mice

Four carcinogenicity studies in CD-1 mice were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 85 mg/kg/day to 4800 mg/kg/day for 18–24 months. In one study there were no statistically significant or otherwise notable increases in the occurrence of any tumor types. Tumors observed in the other three studies are discussed below.

(i) Kidney

Kidney (renal tubular) tumors were seen in male CD-1 mice in one study (MRID No. 00251007). The incidences of adenomas was 1/49 (2%), 0/49 (0%), 0/50 (0%), and 1/50 (2%) in the control (0 mg/k/day), low- (157 mg/kg/day), mid- (814 mg/kg/day) and high-dose (4945 mg/kg/day) groups, respectively. The incidence of carcinomas was 0/49 (0%), 0/49 (0%), 1/50 (2%) and 2/50 (4%) in the control, low-, mid- and high-dose groups, respectively. The incidence of adenomas or carcinoma (combined) was 1/49 (2%), 0/50 (0%), 1/50 (2%), and 3/50 (6%) in the control, low-, mid-, and high-dose groups, respectively. None of these differences showed statistical significance.

The CARC reaffirmed the previous conclusion that the kidney tumors are not treatment-related based on the following weight-of-evidence considerations: a) lack of dose-related trend or statistical significance in pairwise comparisons; b) lack of non-neoplastic renal tubular lesions (*e.g.* tubular necrosis/regeneration, hyperplasia, or basophilia); c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well; and d) the difference in incidence between high-dose group (3/50) and the control group (1/49) was minimal, especially considering the very high concentration given (4 x time the limit dose).

Furthermore, the Pathology Work Group concluded that the renal tumors were not treatment-related since none of the treatment groups differed from the controls for a linear trend or pairwise statistical significance, there was no treatment-related nephrotoxic lesions including pre-neoplastic changes, and multiple renal tumors were not seen in any animal.

In addition, the CARC noted that renal tumors were not observed when tested at a similar dose (4348 mg/kg/day) in this strain of mice in another study(Arysta, 1997b) or in two other studies at the limit dose (MRID No. 49631702, Nufarm, 2009b). If really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000 – 4000 mg/kg/day.

(ii) Lung adenocarcinoma

There was a dose-dependent increase in the incidence of bronchiolar-alveolar adenocarcinoma of the lung in male CD-1 mice (Nufarm, 2009b). There was a positive trend (P=0.02906) in the incidence of lung adenocarcinomas: 5/51 (10%), 5/51 (10%), 7/51 (14%) and 11/51 (22%) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related due to lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions in the lung (*e.g.*, bronchiolar-alveolar hyperplasia), and incidences in all treated groups within the background range (1.42–26%) for this tumor in this strain and age of mice. Also, lung tumors were not seen when tested at a comparable dose (1000 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other three studies (MRID Nos. 00251007; 49631702; Arysta, 1997b).

(iii) Lymphoma/Lymphosarcomas

There was a dose-dependent and statistically significant increase in the incidence of malignant lymphomas in male mice (Nufarm, 2009b). The incidence was: 0/51 (0%; trend P=0.006633), 1/51 (2%), 2/51 (4%) and 5/51 (10%; P=0.02820) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related since the incidences in the concurrent controls (0%) were not representative of the normal background incidences noted in the historical controls (mean, 4.5%; range, 1.5% to 21.7%), and the apparent statistical significance of the pairwise comparison of the high dose group with the concurrent control might have been attributable to this factor rather than an actual carcinogenic response. Also, this neoplasm was not seen in other studies in this strain of mice. For example, in the study by Knezevich and Hogan 1983 (MRID No. 00251007), there was no significant difference in the incidence of lymphomas between control and high-dose groups (P=1.00 for males, P=0.12 for females). In the study by Atkinson *et al.* (1993) (MRID No. 496317), the incidence values in "lymphoreticular/ hematopoietic tissue" were not significantly different between control and high-dose groups (males: 4 in controls, 6 in high-dose group; females: 14 in controls, 13 in high-dose group). In the Arysta 1997 study (Greim *et al.*, 2015), the incidence of lymphoma in males was 2/50, 2/50, 0/51, 6/50 in the control, low, mid and high dose groups, respectively. There were no statistically significant pairwise differences observed in any of these studies.

(iv) Hemangioscarcomas

Hemangiosarcomas were seen in multiple organs including, liver, spleen, and prostate in males and liver and uterus in female CD-1 mice (MRID No. 49631702). There was a positive trend (P=0.00296) in the incidence of hemangiosarcomas in male mice: 0/47 (0%), 0/46 (0%), 0/50 (0%) and 4/45 (9%) at the 0, 100, 300 and 1000 mg/kg/day groups, respectively. The hemangiosarcomas were present in the liver, spleen or prostate in the high dose males. In females, this neoplasm was seen in one female at the low dose (uterus) and in one high dose (spleen). The CARC did not consider the hemangiosarcomas in males to be treatment-related based on the following considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed in mice as spontaneous tumors and are generally more common in males in CD-1 strain mice; 5) there was not a significant increase in hemangiosarcomas seen in the other three mouse studies; and 6) if really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000-4000 mg/kg/day.

In summary, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female CD-1 mice.

C. Discussion

When determining the carcinogenic potential of chemicals, the IARC identifies a cancer "hazard" if an agent (*e.g.*, chemical) is capable of causing cancer under some circumstance and the agent is termed "carcinogenic" if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The IARC also considers that there is "*sufficient evidence of carcinogenicity*" based on the occurrence of increased tumors (benign, malignant, or combination) in: 1) two or more species of animals; 2) two or more independent studies in one species; and/or 3) an increased incidence of tumors in both sexes of a single species. Furthermore, a single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites (IARC Preamble, 2006).

In March 2015, the IARC evaluated the carcinogenic potential of glyphosate. The IARC determined that there was a positive trend in the incidence of a rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. Thus, in accordance with one of the preamble criteria, "the occurrence of tumors in two studies in one species," IARC determined that there is "sufficient evidence" in experimental animals for the carcinogenicity of glyphosate (IARC, 2015).

In contrast, the USEPA's carcinogenicity classification is based on weight-of-evidence considerations in accordance with the agency's 2005 Guidelines for Carcinogen Risk Assessment. The cancer guideline emphasizes the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This evaluation is accomplished in a single integrative step after assessing all of the individual lines of evidence. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiological studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insight into the possible mode(s) of action and likelihood of human cancer hazard and risk (USEPA, 2005).

Conclusions for evidence of carcinogenicity are based on the combined strength and coherence of inferences appropriately drawn from all of the available information. The following observations add significance to the tumor findings: tumors in multiple species, strains, or both sexes; dose-related increases; progression of lesions from pre-neoplastic to benign to malignant; proportion of malignant tumors; reduced latency of neoplastic lesions; and both biological and statistical significance of the findings (USEPA, 2005).

The IARC attributed the kidney tumors observed in male CD-1 mice at the high dose in the feeding study (MRID No. 00251007) to treatment since they are rare and there was borderline significance in trend test (P=0.034 for carcinoma and P=0.037 for combined adenoma or carcinoma) in a Cochran-Armitage trend test. However, as shown in Table 14, the agency's statistical analyses did not show a significant trend for either carcinoma (P=0.06345) or the combined adenoma or carcinoma (P=0.06483). In a Fisher's exact test, when compared to the concurrent control, there was no pairwise significance for any tumor type (adenoma, carcinoma, or combined). There were no pre-neoplastic renal tubular lesions such as tubular necrosis/ regeneration, hyperplasia or hypertrophy, despite a high dose level (4945 mg/kg/day) that was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guidelines. Examination of multiple sections of kidneys from all animals by more than one pathologist did not result in any additional neoplasms. Although the highest dose tested (4945 mg/kg/day) was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guideline, the incidence of the kidney tumors was minimal (1/50 adenomas and 2/50 carcinomas) compared to controls (1/49 adenomas). An evaluation by the PWG concluded that the renal tumors are not treatment-related since there were no compound related nephrotoxic lesions, including pre-neoplastic changes, multiple tumors were not found in any animals, and there was no evidence of a significant linear trend at the 0.5 level in a one-tailed Cochran-Armitage test or pairwise significance in a Fisher's exact test. Furthermore, kidney tumors were not seen when tested at lower (85 to 1000 mg/kg/day) doses or at a comparable (4116 mg/kg/day) dose in this strain of mice in the other three studies. Thus, the totality of data available from 4 carcinogenicity studies provides a strong support for the conclusion that the kidney tumors seen in one study is not the result of a carcinogenic response to glyphosate.

The IARC attributed the hemangiosarcomas observed in male CD-1 mice at the high dose in separate feeding study (MRID No. 49631702) to treatment due to the positive trend (P<0.001) in a Cochran-Armitage trend test. As shown in Table 16, the agency's statistical analyses also showed a positive trend (P=0.00296) in the trend test. In the Fisher's exact test, there was no pairwise significance when compared to controls. In contrast with the IARC, the CARC did not consider the hemangiosarcomas to be treatment-related based on the following weight-of-evidence considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed as spontaneous tumors in male CD-1 strain mice; and 5) hemangiosarcomas were not seen when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other studies (MRID No.00251007, Arysta, 1997b, Nufarm, 2009b). It is noted that JMPR in their evaluation also concluded that the hemangiosarcomas are not treatment-related owing to lack of dose-response relationship, lack of statistical significance and incidences within the historical control range (JMPR, 2004).

Hemangiosarcomas have similar histopathological features in rodents and humans but differ in both incidence and tissue site. In human populations, hemangiosarcomas have an incidence rate of approximately 0.2 new cases/100,000 people (0.0002%) (1996–2000, US National Cancer Institute–SEER Database) and account for <1% of all human sarcomas. The historical background incidence of hemangiosarcomas in B6C3F1 and CD-1 mice relative to the incidence rate in humans has thus been estimated to be approximately 10,000-fold higher than in people (Pegg *et al.,* 2012). The most common sites for spontaneous hemangiosarcomas in rodents are liver, spleen, bone marrow, and to a lesser extent in lymph nodes and skin (see references in Pegg *et al.* (2012). In male mice, liver and spleen tend to be the most common sites. Human hemangiosarcoma is most commonly reported in skin (Weiss *et al*., 2001). Primary liver hemangiosarcoma in humans has been linked to chemical exposure, notably thorotrast and vinyl chloride, which are both considered genotoxic carcinogens. There are several examples of induction of hemangiosarcomas by non-genotoxic agents in mice, but no clear examples of hemangiosarcoma induction by non-genotoxic agents in human populations (Cohen *et al.,* 2009). Several studies have looked at potential mode of action (MOA) for these tumors in mice in response to various drugs or chemicals. These MOAs generally relate to hypoxia or vascular toxicity as early key events.

1. **Mutagenicity**

Glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronucleus assay studies. There is no convincing evidence that the DNA damage is a direct effect of glyphosate, but under some conditions may be secondary to cytotoxicity or oxidative damage. Furthermore, the chemical structure of glyphosate, with its absence of alkyl groups also provides SAR support for the lack of mutagenic/genotoxic potential.

IARC concluded that "there is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic"; however, the IARC analysis included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The CARC did not include such studies in their evaluation. The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay); however, DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited, where positive findings were reported for chromosomal damage, had study limitations confounding the interpretation of the results. In addition, these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. This includes many negative studies cited by Kier and Kirkland (2013) that were considered by CARC, but were not included in the IARC decision.

2. Structure Activity Relationship

Sulfosate (the trimethylsulfonium salt of glyphosate) is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans," based on the lack of evidence of carcinogenicity in mice and rats in two acceptable studies, and absence of mutagenicity concern.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, glyphosate is classified as "Not Likely to be Carcinogenic to Humans." This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Not required.

VIII. BIBLIOGRAPHY

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To: Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]
From: Goodis, Michael
Sent: Fri 5/6/2016 2:46:30 PM
Subject: Glyphosate CARC

Khue

When you get a chance, would you mind sending me the CARC report so I can read it?

I expect to get some questions on it during my next OECD meeting in June so would like to familiarize myself with what is in it. Thanks

Michael Goodis, P.E.

Associate Director, Pesticide Re-evaluation Division (PRD)

Office of Pesticide Programs

Phone 703-308-8157

Mail code 7508P

Room S9624

To: Nguyen, Khue[Nguyen.Khue@epa.gov]; Anderson, Neil[Anderson.Neil@epa.gov]
From: Han, Kaythi
Sent: Mon 5/2/2016 7:44:24 PM
Subject: FW: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

FYI—list of outlets who've inquired about the documents and CBD's press statement.

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 3:39 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: FW: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

Ex. 5 - Deliberative Process

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 3:34 PM
To: Harrison, Melissa <Harrison.Melissa@epa.gov>; Conger, Nick <Conger.Nick@epa.gov>; Perry, Dale <Perry.Dale@epa.gov>
Cc: Hull, George <Hull.George@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

Ex. 5 - Deliberative Process

Outlets asking:

WSJ

Bloomberg

Bloomberg/BNA

Reuters Freelancer

Agi- pulse

Freelancer

http://biologicaldiversity.org/news/press_releases/2016/glyphosate-05-02-2016.html

CENTER for BIOLOGICAL DIVERSITY Because

For Immediate Release, May 2, 2016

Contact: Nathan Donley, (971) 717-6406, ndonley@biologicaldiversity.org

EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

PORTLAND, *Ore.*— An EPA analysis relying heavily on unpublished, industry funded studies has determined that glyphosate, commonly known as Roundup, is "not likely to be carcinogenic to humans." The EPA determination, released to the public on Friday, stands in sharp contrast to a finding last year by the World Health Organization's cancer-research arm that glyphosate is a probable human carcinogen.

"EPA's determination that glyphosate is non-carcinogenic is disappointing, but not terribly surprising — industry has been manipulating this process for years," said Nathan Donley, a scientist with the Center for Biological Diversity. "The analysis done by the World Health Organization is more open and transparent and remains the gold standard."

The EPA's analysis relied heavily on industry-funded studies that have not undergone public scrutiny, while the WHO used publically available research for its analysis. Furthermore, the WHO took into account studies on actual products that are available on store shelves, while the EPA ignored those studies to focus solely on studies that tested glyphosate as a single ingredient. Most products containing glyphosate have other ingredients that can make the pesticide more dangerous.

"We shouldn't gamble with the risk of cancer and must take appropriate precautions until we get a conclusive answer about the true dangers of glyphosate," said Donley. "The indiscriminate drenching of farms, ball fields and backyards with glyphosate needs to end."

The EPA's industry-friendly determination comes amid a fierce debate in Europe and the United States over the safety of glyphosate.

In February 35 members of the U.S. House of Representatives sent a letter to EPA Administrator Gina McCarthy expressing concerns regarding the potential negative health and environmental impacts of a pesticide, Enlist Duo, that combines glyphosate and 2,4-D. The agency is currently reanalyzing its decision to register the dangerous pesticide after it was revealed that the industry had withheld data on how the pesticides work in combination with other ingredients to have a stronger effect on the environment.

This finding comes as the EPA is in undertaking a "registration review" of glyphosate, a process designed to determine whether the chemical can safely be used in light of new scientific research. These documents will inform the agency's decision on whether to allow glyphosate to be used for the next 15 years. The last time the EPA fully analyzed the threats posed by glyphosate was 1993.

The Center for Biological Diversity is a national, nonprofit conservation organization with more than 1 million members and online activists dedicated to the protection of endangered species and wild places.

Alaska . Arizona . California . Florida . Minnesota . Nevada . New Mexico . New York . Oregon . Vermont . Washi

P.O. Box 710 . Tucson, AZ 85702-0710 *tel:* (520) 623.5252 *fax:* (520) 623.9797 *www.BiologicalDiv*

To: Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Perron, Monique[Perron.Monique@epa.gov]; Bloem, Thomas[Bloem.Thomas@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Mon 5/2/2016 6:46:52 PM
Subject: RE: glyphosate: bibliography follow up

Hi Khue:

We'll get back to you soon.

Thanks,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Monday, May 02, 2016 12:46 PM
To: JENKINS, DANIEL J [AG/1920]
Cc: Anderson, Neil; Moriarty, Thomas; Perron, Monique; Bloem, Thomas; Dunbar, Anwar; Smith, Charles
Subject: glyphosate: bibliography follow up
Importance: High

Hi Dan,

I hope you had a good weekend. The team has screened the bibliographies that Monsanto sent earlier in April at EPA's request. Attached please find the initial list of studies that we are requesting. Another list is forthcoming and we will send it once available. Whenever possible, please forward study reports in English. We noticed that some of the genotoxicity studies were in Spanish—are English versions available? Same with some of the Japanese studies from the TAC list.

As you know, this matter is time-sensitive, please send the studies as soon as possible directly to me either electronically or via CD submission. Please also be sure to reformat these studies and submit them formally through front end processing, when you get a chance later, so they can be assigned MRID numbers and tracked in our system.

We really appreciate Monsanto's willingness to address this information request. Let us know if you have any questions.

Thanks!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

To: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Perron, Monique[Perron.Monique@epa.gov]; Bloem, Thomas[Bloem.Thomas@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]
From: Nguyen, Khue
Sent: Mon 5/2/2016 4:45:32 PM
Subject: glyphosate: bibliography follow up
5.2.16 EPA list of studies requested.docx

Hi Dan,

I hope you had a good weekend. The team has screened the bibliographies that Monsanto sent earlier in April at EPA's request. Attached please find the initial list of studies that we are requesting. Another list is forthcoming and we will send it once available. Whenever possible, please forward study reports in English. We noticed that some of the genotoxicity studies were in Spanish—are English versions available? Same with some of the Japanese studies from the TAC list.

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We really appreciate Monsanto's willingness to address this information request. Let us know if you have any questions.

Thanks!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

5/2/16—List of studies being requested by EPA

A subset of studies from Monsanto's bibliography of tox studies submitted to BfR for EU Annex 1 Renewal:

KIIA 5.1.1 (OECD)	Blech, S.; Stratmann, A.	1995	Glyphosate: ADME-study in rats - Final report A&M 038/94, TOX9552251
KIIA 5.1.1 (OECD)	Knowles, S.L.; Mookherjee, C.R.	1996	[14C]-glyphosate: Absorption, distribution, metabolism and excretion following oral administration to the rat 1413/2-1011 NUF GLP: Y, published: N 2309072 / ASB2012-11380
KIIA 5.1.1 (OECD)	Leuschner, J.	1995	Metabolism study of 14C-labelled glyphosate after single oral and intravenous administration to Sprague-Dawley rats, 9202/95 TOX9650071
KIIA 5.1.1 (OECD)	McEwen, A.B.	1995	HR-001: Metabolism in the rat SNY 332/951256 HLS GLP: Y, published: N 2309070 / ASB2012-11379
KIIA 5.1.1 (OECD)	Powles, P.; Hopkins, R.	1992	(14C)-glyphosate: Absorption and distribution in the rat - preliminary study TOX9552358
KIIA 5.1.1 (OECD)	Powles, P.; Hopkins, R.	1992	(14C)-glyphosate: Absorption, distribution, metabolism and excretion in the rat, TOX9300343
KIIA 5.4.4 KIIA 5.10 (OECD)	Chruscielska, K.; Brzezinski, J.; Grafstein, B.	2000	Glyphosate: Evaluation of chronic activity and possible far -reaching effects - Part 2. Studies on mutagenic activity Pestycydy, 2000, (3-4), 21-25 ASB2013-9830
KIIA 5.5.2 (OECD)	Enomoto, A.	1997	HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 1 (Seite 1- 500) IET 94-0150 Vol.1 ALS GLP: Y, published: N 2309360 / ASB2012-11484
KIIA 5.5.2 (OECD)	Enomoto, A.	1997	HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 2 (Seite 501-1000) IET 94-0150 Vol. 2 ALS GLP: Y, published: N 2309362 / ASB2012-11485
KIIA 5.5.2 (OECD)	Enomoto, A.	1997	HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol.3 (Seite 1001-1500) IET 94-0150 Vol. 3 ALS GLP: Y, published: N 2309364 / ASB2012-11486
KIIA 5.5.2 (OECD)	Enomoto, A.	1997	HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 4 (Seite 1501-2051) IET 94-0150 Vol. 4 ALS GLP: Y, published: N 2309366 / ASB2012-11487
KIIA 5.5.2 (OECD)	Suresh, T.P.	1996	Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats TOXI:886.C.C-R FSG GLP: Y, published: N 2309343 / TOX9651587 / TOX9600015
KIIA 5.5.2 (OECD)	Wood, E., Dunster, J., Watson, P.	2009	Glyphosate Technical: Dietary combined chronic toxicity / carcinogenicity study in the rat SPL2060-0012 NUF

	Brooks, P.		GLP: Y, published: N 2309391 / ASB2012-11490
KIIA 5.5.3 (OECD)	Kumar, D.P.S.	2001	Carcinogenicity Study with Glyphosate Technical in Swiss Albino Mice TOXI: 1559.CARCI-M FSG GLP: Y, published: N 2309396 / ASB2012-11491
KIIA 5.5.3 (OECD)	Sugimoto, K.	1997	HR-001: 18-Month Oral Oncogenicity Study in Mice IET 940151 ALS GLP: Y, published: N 2309415 / ASB2012-11493
KIIA 5.5.3 (OECD)	Wood, E., Dunster, J., Watson, P., Brooks, P.	2009	Glyphosate Technical: Dietary carcinogenicity study in the mouse SPL 2060-0011 NUF GLP: Y, published: N 2309412 / ASB2012-11492
KIIA 5.6.2 (OECD)	Wood, E.	2011	Glyphosate Technical: Dietary carcinogenicity study in the mouse – Amendment SPL 2060-0011 ASB2014-9149
KIIA 5.6.2 (OECD)	Wood, E.	2011	Assessment and further discussion on rele- vance of perceived elevation in testicular atro- phy for SafePharm project number 2060/0011 (Glyphosate technical: mouse oncogenicity study) SPL 2060-0011 ASB2014-9150
KIIA 5.10 (OECD)	Takahashi, H.; Kakinuma, Y.	1992	Ammonium salt of glyphosate (MON 8750) general pharmacology study IET 90-0149/ET-92-15 TOX9552421
KIIA 5.10 (OECD)	Wood, E.	1996	Glyphosate Technical: Pharmacology Screening Study in the Rat 434/021 NUF GLP: Y, published: N 2310134 / ASB2012-12054

All studies from Monsanto's bibliography of genotoxicity studies on Monsanto glyphosate formulations:

Ames/Salmonella Mutagenicity Assay of MON 2139 (ROUNDUP®Herbicide Formulation). Kier, L.D., Stegeman, S.D., Costello, J.G., Schermes, S. MSL-11729; EHL91183/ML-91-440. February 7, 1992.

Mouse Micronucleus Study of ROUNDUP®Herbicide Formulation. Kier, L.D., Flowers, L.J., Huffman, M.B. EHL 91200/91204; /ML-91-434/ML-91-437. February 25, 1992.

MON 8709 Teste de Mutacao Genica Reversa (Teste de Ames). Renata Cristina Viana Silvino. RL81984AM; 19700/2010 – 16.0AM. August 8, 2011.

MON 8709 Teste do Micronucleo em Medula Ossea de Camundongo. Flavia Thomazotti Calaro. RL81985MN; 19700/2010 – 17.0MN.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 14420 (Teste de Ames). Marise Ferro Carvalho Marques. RF-G11.19/99. 12/01/ 2000.

Estudo do Micronucleo em Medula Ossea de Camundongo para MON 14420. Marise Ferro Carvalho Marques. RF-G12.36/99. 01/09/1999.

Ames/Salmonella Mutagenicity Assay of MON 14445 DIRECT®Herbicide Formulation). Kier, L.D., Stegeman, S.D., Costello, J.G., Schermes, S. MSL – 11731; EHL 91185/ML-91-442. February 7, 1992.

Mouse Micronucleus Study of DIREC ®Herbicide Formulation. Kier, L.D., Flowers, L.J., Huffman, M.B. EHL 91202/91206; /ML-91-436/ML-91-439. February 25, 1992.

The Salmonella typhimurium reverse mutation by ROUNDUP WG. BioAgri Report # G.1.1 – 011/98. April 02, 1998.

A micronucleus study in mice for ROUNDUP WG. BioAgri Report # G.1.2 – 59/97. August 22, 1998.

Bacterial Reverse Mutation Assay with a Confirmatory Assay. MON 76313. Michael Mecchi. Covance Study Number 6103-757; Monsanto Study Number CV-08-242. 24 November 2008.

In Vivo Mouse Bone Marrow Micronucleus Assay. MON 76313. Yong Xu. Covance Study Number 6103-758; Monsanto Study Number CV-08-243. 03 December 2008.

MON 76313 Teste de Mutacao Genica Reversa (Teste de Ames). Renata Cristina Viana Silvino. RL108867AM; 11241/2011 – 5.0AM. March 1, 2012.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 77063. Marise Ferro Carvalho Marques. RF-G11.59/98. 12/07/ 1999.

Teste de Micronucleo em para MON 77063 em camundongos. Marise Ferro Carvalho Marques. RF-G12.16/99. May 7, 1999.

The Salmonella typhimurium reverse mutation by MON 77280. BioAgri Report # G.1.1 – 046/97. March 05, 1998.

A micronucleus study in mice for MON 77280. BioAgri Report # G.1.2 – 48/97. February 20, 1998.

MON 77280 Bacterial Reverse Mutation Test (Ames Test). Mara Rubia Camolesi. RL42517AM-B; 12208/2009 – 3.0AM.

MON 77280 Teste de Mutacao Genica Reversa em *Salmonella typhimurium* (Teste de Ames). Mara Rubia Camolesi. RL42517AM; 12208/2009 – 3.0AM. April 8, 2010.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 77391. Marise Ferro Carvalho Marques. RF-G11.60/98. 15/07/ 1999.

Teste de Micronucleo em para MON 77391 em camundongos. Marise Ferro Carvalho Marques. RF-G12.17/99. May 11, 1999.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 78036. Valeria C. Franco Perina. RF-G11.62/98. 12 November 1999.
Teste de Micronucleo para MON 78036 em camundongos. Marise Ferro Carvalho Marques. RF-

G12.19/99. 12 May 1999.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 78091 (Teste de Ames). Marise Ferro Carvalho Marques. RF-G11.18/99. 12/01/2000.

Estudo do Micronucleo em Medula Ossea de Camundongos para MON 78091. Marise Ferro Carvalho Marques. RF-G12.35/99. 01/09/1999.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 78128 (Teste de Ames). Marise Ferro Carvalho Marques. RF-G11.42/99. 25/10/1999.

Estudo do Micronucleo em Medula Ossea de Camundongos para MON 78128. Marise Ferro Carvalho Marques. RF-G12.64/99. 25/11/1999.

MON 78239: *Salmonella – Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with Confirmatory Assay. Michael Mecchi. Covance Study Number 6103-355; Monsanto Study Number CV-2002-186. April 16, 2003.

In Vivo Mouse Bone Marrow Micronucleus Assay with MON 78239. Gregory Erexson. Covance Study Number 6103-352; Monsanto Study Number CV-2002-187. 24 April 2003.

MON 78634: *Salmonella – Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with Confirmatory Assay. Michael Mecchi. Covance Study Number 6103-354; Monsanto Study Number CV-2002-188. April 16, 2003.

In Vivo Mouse Bone Marrow Micronucleus Assay with MON 78634. Gregory Erexson. Covance Study Number 6103-353; Monsanto Study Number CV-2002-189. 24 April 2003.

Salmonella – Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with MON 78910. Yong Xu. Covance Study Number 6103-511; Monsanto Study Number CV-2005-119. 01 March 2006.

In Vivo Mouse Bone Marrow Micronucleus Assay. MON 78910. Gregory Erexson. Covance Study Number 6103-512; Monsanto Study Number CV-2005-120. 01 March 2006.

Bacterial Reverse Mutation Assay with a Confirmatory Assay. MON 79864. Michael Mecchi. Covance Study Number 6103-745; Monsanto Study Number CV-08-030. 09 September 2008.

In Vivo Mouse Bone Marrow Micronucleus Assay. MON 79864. Yong Xu. Covance Study Number 6103-746; Monsanto Study Number CV-08-031. 07 October 2008; Amended 03 March 2011.

Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay. MON 79991. Michael Mecchi. Covance Study Number 6103-709; Monsanto Study Number CV-2007-082. 30 January 2009.
In Vivo Mouse Bone Marrow Micronucleus Assay with MON 79991. Yong Xu. Covance Study

Number 6103-708; Monsanto Study Number CV-2007-083. 23 January 2009.

The following studies from "List of Studies from TAC Group":

1	DPC/AE-1604-2	Metabolism Study in Rats with AK-01(Glyphosate) Technical(Definitive Study)	Daiichi Pure Chemicals Co., Ltd	Matsuo Takaichi	1992	Full report	J
	DPC/AE-1604-2	Metabolism Study in Rats with AK-01(Glyphosate) Technical(Preliminary Study)	Daiichi Pure Chemicals Co., Ltd	Matsuo Takaichi	1992	Full report	J
12-1	H-95053	Oral Feeding Combined Chronic Toxicity/Carcinogenicity Study in Rats with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Michiko Takahashi	1999	Narrative Part	J/E
						Summary data	E
						Appendix	E
						Histopathological Evaluation/ narrative part	J/E
						Histopathological Evaluation/ Individuals	E
12-2		Pathology Working Group Review of the Histopathologic Changes in the Kidney: A Combined Chronic Toxicity/Carcinogenicity Study of Glyphosate in Rats; Study No.H-95053	Experimental Pathology Laboratories, Inc.	Jerry F. Hardisty	2013	Narrative Part	E
							J
						Appendix	E
13-1	H-95056	Oral Feeding Carcinogenicity Study in Mice with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Michiko Takahashi	1999	Narrative Part	J/E
						Summary data	E
						Appendix	E
13-2	H-95056	Addendum: Statement on Tumourigenicity of AK-01(Glyphosate) Technical in Mouse Kidneys	Nippon Experimental Medical Research	Michiko Takahashi	1999	Full report	J/E
23		**General Pharmacology Studies with AK-01(Glyphosate) Technical**	**Iwate Medical University**	**Tadanobu Ito**	**1992**	**Full report**	**J**

To: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]; HEERING, DAVID C [AG/1000][david.c.heering@monsanto.com]; HEYDENS, WILLIAM F [AG/1000][william.f.heydens@monsanto.com]; NYANGULU, JAMES M [AG/1920][james.m.nyangulu@monsanto.com]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Lowit, Anna[Lowit.Anna@epa.gov]; Perron, Monique[Perron.Monique@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Bloem, Thomas[Bloem.Thomas@epa.gov]
From: Nguyen, Khue
Sent: Thur 4/28/2016 8:40:07 PM
Subject: RE: notes from April 5 glyphosate meeting
glyphosate monsanto meeting notes corrected 4.28.16.docx

Hi Dan,

I recently got back from vacation and I'm catching up on all the email traffic. Thanks for the bibliography. We appreciate Monsanto's prompt response. I am attaching the corrected meeting notes (with suggestions incorporated) for your records. These notes, along with the sign-in sheet which we sent before, will be posted to the public docket at www.regulations.gov.

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Monday, April 18, 2016 8:28 AM

To: Nguyen, Khue <Nguyen.Khue@epa.gov>; LISTELLO, JENNIFER J [AG/1000] <jennifer.j.listello@monsanto.com>; HEERING, DAVID C [AG/1000] <david.c.heering@monsanto.com>; HEYDENS, WILLIAM F [AG/1000] <william.f.heydens@monsanto.com>; NYANGULU, JAMES M [AG/1920] <james.m.nyangulu@monsanto.com>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Moriarty, Thomas <Moriarty.Thomas@epa.gov>; Smith, Charles <Smith.Charles@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>; Perron, Monique <Perron.Monique@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>
Subject: RE: notes from April 5 glyphosate meeting

Hi Khue:

We made some minor corrections in the notes, please see the attached version.

Also, per EPA's request at the 4/6/16 meeting, see attached tox study bibliography which represents the overwhelming majority of studies on glyphosate and glyphosate formulations. Later this week, we anticipate providing a list of additional studies that were done on final formulations as well as the a.i., that BfR (the EU rapporteur) did not review because they were only submitted in non-EU countries.

Regarding EPA's formulation questions in your prior email, and as discussed in the meeting on 4/6/16, our answer is below:

For the glyphosate epidemiology studies noted by EPA, the results were published in the scientific literature during the 2001 – 2009 timeframe; data capture for these studies would have terminated a few years prior to the publication dates (factoring in time to organize/analyze results, perform statistics, write the publications, complete the peer-review process, etc.). Thus, the exposures to the applicators in these studies that are most relevant likely occurred in the 1990s and 1980s. The surfactant system used almost exclusively in Roundup agricultural herbicide formulations globally throughout these two decades contained a polyethoxylated tallow amine surfactant (some phosphate ester surfactant usage began in the late 1990s). Rather, differences in study size and experimental design/analysis (e.g., consideration of potential exposure and controlling for bias/confounding factors) are considered to be responsible for the apparent differing results.[*1,2]

*1: Final Addendum to the renewal assessment report on glyphosate, compiled by EFSA, October 2015. http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302

*2: EFSA explains the carcinogenicity assessment of glyphosate: http://www.efsa.europa.eu/sites/default/files/4302_glyphosate_complementary.pdf

Thanks and please let us know if you have any questions.

Best Regards,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Wednesday, April 06, 2016 2:57 PM
To: JENKINS, DANIEL J [AG/1920]; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Moriarty, Thomas; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: notes from April 5 glyphosate meeting

Hi all,

Thanks for attending the meeting on glyphosate yesterday. We thought it was a very productive discussion. Attached, please find the notes from the meeting and the sign-in sheet for your records. Please feel free to send edits/corrections for the notes if you feel that EPA has mischaracterized anything.

The notes outline the information that HED requested during the meeting yesterday. As you know, this information request is time sensitive—**would it be possible for Monsanto to send the bibliography that was discussed by April 15th?**

Also, as a side note, in the email to Monsanto dated 3/31/16, the list of epi studies gives the impression that there were 12 studies cited, but we double checked and it was a copy/paste error and there are only 6 epi studies.

Thanks again for being so responsive to our request for information.

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

Glyphosate: 4/5/16 meeting between EPA and Monsanto—notes

EPA met with Monsanto to discuss EPA's recent information request for glyphosate. In an email dated 3/21/16, EPA requested information on the inert ingredients used in popular US and European formulations of glyphosate in the present day and also dating back to the 80s. EPA was particularly interested in information on how glyphosate formulations have changed over time in the last 20-30 years. In its email request, EPA included a list of 6 epi studies that were completed in the mid-1980s to the early 2000s; these studies were cited in the IARC's recent report on glyphosate. EPA included this list of studies because it was interested in characterizing potential differences in US and European glyphosate epidemiology studies.

Monsanto briefly discussed the epi studies that were referenced in EPA's 3/21/16 email and discussed why they are not suitable to assess the carcinogenicity of glyphosate. Monsanto also briefly discussed glyphosate's history of safety and the conclusions of various regulatory agencies all over the world, many of which conclude that glyphosate was not carcinogenic.

EPA stated that at this time it was not interested in discussing the opinions of other regulatory agencies nor was it interested in debating glyphosate's alleged carcinogenicity at the April 5 meeting. Rather, EPA stated that it was in the midst of a large scale holistic review of the glyphosate database. EPA's approach for registration review risk assessment is to take a systematic and scientific, weight of the evidence approach, and would not rely on the regulatory conclusions of other regulatory agencies. In an effort to resolve questions about the potential toxicity of glyphosate, glyphosate formulations, and any co-formulants (inert ingredients and surfactants), EPA was interested in any data or information Monsanto may have on how the formulations may differ from data on the active ingredient and surfactants independently of one another.

Of particular interest to EPA are the following:

1) Toxicity (particularly repeat dose data) or pharmacokinetic formulation studies.
2) Information on the pharmacokinetics of glyphosate, including info on tissue dosimetry or metabolism.
3) *In vitro* studies on bioactivity (including cellular-based bioactivity).
4) Any *in vitro* ADME (absorption, distribution, metabolism, and excretion) studies
5) Any remaining carcinogenicity studies on glyphosate not yet submitted to EPA. At some point in the future, the agency may be interested in other toxicities (*e.g.*, developmental or reproductive toxicity).

EPA requested that rather than sending to the agency all the studies that might be relevant, Monsanto should start with a bibliography that EPA can use to compare with its own bibliography. The agency requested that Monsanto include data generated for both North American registrations as well as European registrations. Then EPA would be able to indicate which of these studies would be of potential use in its analysis and make a request for them. EPA indicated that this should be done as soon as possible.

There was also some discussion about changes in Monsanto's Roundup formulation over the years. Monsanto indicated that up until 2000, nearly all glyphosate products on the market were its Roundup formulation which used some form of tallow amine as a surfactant. Afterwards, the properties of

surfactants used and the ratio of surfactant to active ingredient were changed in most formulations due to a need for increased ai loading. Current products vary geographically due to various reasons, some having to do with marketing. EPA suggested that Monsanto provide in writing any information that documents the changes of glyphosate formulations over time and across the globe.

The agency appreciates Monsanto's cooperation in its attempt to conduct a thorough and transparent science-driven analysis of the human health effects of glyphosate under registration review.

To: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Nguyen, Khue[Nguyen.Khue@epa.gov]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]; HEERING, DAVID C [AG/1000][david.c.heering@monsanto.com]; HEYDENS, WILLIAM F [AG/1000][william.f.heydens@monsanto.com]; NYANGULU, JAMES M [AG/1920][james.m.nyangulu@monsanto.com]
Cc: Smith, Charles[Smith.Charles@epa.gov]; Lowit, Anna[Lowit.Anna@epa.gov]; Perron, Monique[Perron.Monique@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Bloem, Thomas[Bloem.Thomas@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Thur 4/21/2016 6:06:43 PM
Subject: RE: notes from April 5 glyphosate meeting
TAC Studies_List.pdf

Hi Neil:

This should be last one. These were submitted to the Japanese authorities for their review.

Again, let us know if you have any questions.

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Anderson, Neil [mailto:Anderson.Neil@epa.gov]
Sent: Wednesday, April 20, 2016 11:37 AM
To: JENKINS, DANIEL J [AG/1920]; Moriarty, Thomas; Nguyen, Khue; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]

Cc: Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: RE: notes from April 5 glyphosate meeting

Thank you Dan. We will let you know if we have any follow-up questions.

Regards,

Neil Anderson

Chief, Risk Management and Implementation Branch I

Pesticide Re-evaluation Division, Office of Pesticide Programs

US EPA (Mail Code 7508P)

1200 Pennsylvania Avenue, NW

Washington, DC 20460

Phone: 703-308-8187

anderson.neil@epa.gov

Visit us on the Web at: http://www.epa.gov/pesticides/

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Wednesday, April 20, 2016 11:10 AM
To: JENKINS, DANIEL J [AG/1920] <daniel.j.jenkins@monsanto.com>; Moriarty, Thomas <Moriarty.Thomas@epa.gov>; Nguyen, Khue <Nguyen.Khue@epa.gov>; LISTELLO, JENNIFER J [AG/1000] <jennifer.j.listello@monsanto.com>; HEERING, DAVID C [AG/1000] <david.c.heering@monsanto.com>; HEYDENS, WILLIAM F [AG/1000] <william.f.heydens@monsanto.com>; NYANGULU, JAMES M [AG/1920]

<james.m.nyangulu@monsanto.com>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Smith, Charles <Smith.Charles@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>; Perron, Monique <Perron.Monique@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>
Subject: RE: notes from April 5 glyphosate meeting

All:

Here is the additional list of studies I mentioned below. Please let us know if you have any questions.

Thanks,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: JENKINS, DANIEL J [AG/1920]
Sent: Tuesday, April 19, 2016 1:37 PM
To: 'Moriarty, Thomas'; Nguyen, Khue; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: RE: notes from April 5 glyphosate meeting

All:

We are not aware of any additional similar data submitted to Health Canada and not EPA.

Thank you,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Moriarty, Thomas [mailto:Moriarty.Thomas@epa.gov]
Sent: Monday, April 18, 2016 8:39 AM
To: JENKINS, DANIEL J [AG/1920]; Nguyen, Khue; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: RE: notes from April 5 glyphosate meeting

Thank you Dan,

If you can, please confirm that there isn't similar data that Monsanto may have generated/submitted to Health Canada which would also be of interest to us.

Thank you for this, we'll be in touch,

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Monday, April 18, 2016 8:28 AM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>; LISTELLO, JENNIFER J [AG/1000] <jennifer.j.listello@monsanto.com>; HEERING, DAVID C [AG/1000] <david.c.heering@monsanto.com>; HEYDENS, WILLIAM F [AG/1000] <william.f.heydens@monsanto.com>; NYANGULU, JAMES M [AG/1920] <james.m.nyangulu@monsanto.com>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Moriarty, Thomas <Moriarty.Thomas@epa.gov>; Smith, Charles <Smith.Charles@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>; Perron, Monique <Perron.Monique@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>
Subject: RE: notes from April 5 glyphosate meeting

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*2: EFSA explains the carcinogenicity assessment of glyphosate: http://www.efsa.europa.eu/sites/default/files/4302_glyphosate_complementary.pdf

Thanks and please let us know if you have any questions.

Best Regards,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Wednesday, April 06, 2016 2:57 PM

To: JENKINS, DANIEL J [AG/1920]; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Moriarty, Thomas; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: notes from April 5 glyphosate meeting

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Thanks again for being so responsive to our request for information.

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

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List of Studies from TAC GROUP

No.	Report No.	Title of Study	Testing Facility	Study Director	Year of Report	Contents	Language**
1	DPC/AE-1604-2	Metabolism Study in Rats with AK-01(Glyphosate) Technical(Definitive Study)	Daiichi Pure Chemicals Co., Ltd	Matsuo Takaichi	1992	Full report	J
	DPC/AE-1604-2	Metabolism Study in Rats with AK-01(Glyphosate) Technical(Preliminary Study)	Daiichi Pure Chemicals Co., Ltd	Matsuo Takaichi	1992	Full report	J
2	90-Ⅰ A2-1105	Acute Oral Toxicity Study in Rats with AK-01(Glyphosate) Technical	Lifescience Laboratories, Ltd.	Hitoshi Yamamoto	1991	Full report	J
3	90-Ⅰ A1-1103	Acute Oral Toxicity Study in Mice with AK-01(Glyphosate) Technical	Lifescience Laboratories, Ltd.	Atsunobu Matsuo	1991	Full report	J
4	90-Ⅰ G2-0101	Acute Dermal Toxicity Study in Rats with AK-01(Glyphosate) Technical	Lifescience Laboratories, Ltd.	Atsunobu Matsuo	1991	Full report	J
5	9201	Acute Inhalation Toxicity Study in Rats with AK-01(Glyphosate) Technical	Research Institute, MECT Corporation	Atsuko Takahashi	1992	Full report	J
6	FMB 03-5153	Dermal Sensitization Study(GPM method) in Guinea Pigs with AK-01(Glyphosate) Technical	Fuji Biomedix Co., Ltd.	Masaru Ishihara	2004	Full report	J
7	91-Ⅱ A2-0102	Subchronic Oral Toxicity Study in Rats with AK-01(Glyphosate) Technical	Lifescience Laboratories, Ltd.	Junji Matsuda	1992	Full report	J
8	H-95052	13 week Rangefinding Study for Oral Feeding Combined Chronic Toxicity/Carcinogenicity Study in Rats with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Michiko Takahashi	1996	Full report	J
9	H-95055	13 week Oral Feeding Subchronic Toxicity Study in Mice with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Michiko Takahashi	1996	Full report	J
	H-95054	2 week Oral Feeding Rangefinding Study in Mice with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Michiko Takahashi	1995	Full report	J

** J: Japanese E: English

List of Studies from TAC GROUP

No.	Report No.	Study Title	Testing Facility	Study Director	Year of Report	Contents	Language**
10	H-95058	13 week Oral Subchronic Toxicity Study in Dogs with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Isao Teramoto	1996	Full report	J
	H-95057	2 week Rangefinding Study for Oral Toxicity Study in Dogs with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Isao Teramoto	1995	Full report	J
11	H-95059	12 month Chronic Oral Toxicity Study in Dogs with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Isao Teramoto	1998	Narrative Part	J/E
						Figures and Tables	E
						Appendix	E
12-1	H-95053	Oral Feeding Combined Chronic Toxicity/Carcinogenicity Study in Rats with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Michiko Takahashi	1999	Narrative Part	J/E
						Summary data	E
						Appendix	E
						Histopathological Evaluation/ narrative part	J/E
						Histopathological Evaluation/ Individuals	E
12-2		Pathology Working Group Review of the Histopathologic Changes in the Kidney: A Combined Chronic Toxicity/Carcinogenicity Study of Glyphosate in Rats; Study No.H-95053	Experimental Pathology Laboratories, Inc.	Jerry F. Hardisty	2013	Narrative Part	E
							J
						Appendix	E
13-1	H-95056	Oral Feeding Carcinogenicity Study in Mice with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research Institute	Michiko Takahashi	1999	Narrative Part	J/E
						Summary data	E
						Appendix	E
13-2	H-95056	Addendum: Statement on Tumourigenicity of AK-01(Glyphosate) Technical in Mouse Kidneys	Nippon Experimental Medical Research	Michiko Takahashi	1999	Full report	J/E
13-3	H-95056	Response to the Questions from Pesticide Expert Panel of Food Safety Commission (held on 2012/12/20)	Taksaki Pathologic Center Co., Ltd.	Masamine Aiuchi	2012	Full report	J/E
14	91-Ⅶ-0101	Bacterial Reverse Mutation Assay with AK-01(Glyphosate) Technical	Lifescience Laboratories, Ltd.	Kouichiro Koyabu	1991	Full report	J/E

** J: Japanese E: English

List of Studies from TAC GROUP

No.	Report No.	Study Title	Testing Facility	Study Director	Year of Report	Contents	Language**
15	91-Ⅶ-0903	*In Vitro* Mammalian Cell Cytogenics Study with AK-01(Glyphosate) Technical	Lifescience Laboratories, Ltd.	Toyonari Araki	1992	Full report	J/E
16	91-Ⅶ-0902	Bacterial DNA Repair Test(Rec-Assay) with AK-01(Glyphosate) technical	Lifescience Laboratories, Ltd.	Toyonari Araki	1992	Full report	J/E
17	FBM 03-8152 (1),(2)	Micronucleus Test in Mice with AK-01(Glyphosate) Technical and Its Range Finding Study	Fuji Biomedix Co., Ltd.	Tatsuo Inoue	2004	Full report	J/E
18	H-95060	2 Generation Oral Feeding Reproduction Study in Rats with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research	Michiko Takahashi	1997	Full report	J
	H-95098	Rangefinding Study for Oral Feeding Reproduction Study in SD Rats with AK-01(Glyphosate) Technical	Nippon Experimental Medical Research	Michiko Takahashi	1995	Full report	J
19	91-ⅣA2-0101	Developmenta Toxicity Study in Rats with AK-01(Glyphosate) Technical	Lifescience Laboratories, Ltd.	Hitoshi Yamamoto	1992	Full report	J
20	91-ⅣA4-0102	Developmental Toxicity Study in Rabbtis with AK-01(Glyphosate) Techncial	Lifescience Laboratories, Ltd.	Atsunobu Matsuo	1992	Full report	J
21	91-Ⅺ A8-0101	Acute Delayed Neurotoxicity Study in Hen with AK-01(Glyphosate) Technical	Lifescience Laboratories, Ltd.	Yukio Yanagimoto	1992	Full report	J
22	FMB 03-2150	90 Day Oral Feeding Neurotoxicity Study in Rats with AK-01(Glyphosate) Technical	Fuji Biomedix Co., Ltd.	Kouichi Neda	2004	Full report	J
23		General Pharmacology Studies with AK-01(Glyphosate) Technical	Iwate Medical University	Tadanobu Ito	1992	Full report	J

** J: Japanese E: English

To: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Nguyen, Khue[Nguyen.Khue@epa.gov]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]; HEERING, DAVID C [AG/1000][david.c.heering@monsanto.com]; HEYDENS, WILLIAM F [AG/1000][william.f.heydens@monsanto.com]; NYANGULU, JAMES M [AG/1920][james.m.nyangulu@monsanto.com]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Lowit, Anna[Lowit.Anna@epa.gov]; Perron, Monique[Perron.Monique@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Bloem, Thomas[Bloem.Thomas@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Wed 4/20/2016 3:10:04 PM
Subject: RE: notes from April 5 glyphosate meeting
Genotoxicity Studies on Monsanto Glyphosate Formulations.pdf
Additional Genotoxicity References 041916.pdf

All:

Here is the additional list of studies I mentioned below. Please let us know if you have any questions.

Thanks,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: JENKINS, DANIEL J [AG/1920]
Sent: Tuesday, April 19, 2016 1:37 PM
To: 'Moriarty, Thomas'; Nguyen, Khue; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]

Cc: Anderson, Neil; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: RE: notes from April 5 glyphosate meeting

All:

We are not aware of any additional similar data submitted to Health Canada and not EPA.

Thank you,

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Suite 450 East
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Office: 202-383-2851

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From: Moriarty, Thomas [mailto:Moriarty.Thomas@epa.gov]
Sent: Monday, April 18, 2016 8:39 AM
To: JENKINS, DANIEL J [AG/1920]; Nguyen, Khue; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: RE: notes from April 5 glyphosate meeting

Thank you Dan,

If you can, please confirm that there isn't similar data that Monsanto may have generated/submitted to Health Canada which would also be of interest to us.

Thank you for this, we'll be in touch,

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Monday, April 18, 2016 8:28 AM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>; LISTELLO, JENNIFER J [AG/1000] <jennifer.j.listello@monsanto.com>; HEERING, DAVID C [AG/1000] <david.c.heering@monsanto.com>; HEYDENS, WILLIAM F [AG/1000] <william.f.heydens@monsanto.com>; NYANGULU, JAMES M [AG/1920] <james.m.nyangulu@monsanto.com>
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From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Wednesday, April 06, 2016 2:57 PM
To: JENKINS, DANIEL J [AG/1920]; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
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Chemical Review Manager

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Additional Genotoxicity References

Gohre K, Casida JE, Ruzo LO. 1987. N oxidation and cleavage of the amino acid derived herbicide glyphosate and anilino acid of the insecticide fluvalinate. J Agric Food Chem. 35:388-392.

Guilherme S, Gaivao I, Santos MA, Pacheco M. 2012a. DNA damage in fish (*Anguilla anguilla*) exposed to a glyphosate-based herbicide - elucidation of organ-specificity and the role of oxidative stress. Mutat Res Genet Toxicol Environ Mutagen. 743:1-9.

Guilherme S, Santos MA, Gaivao I, Pacheco M. 2014a. Are DNA-damaging effects induced by herbicide formulations (Roundup® and Garlon®) in fish transient and reversible upon cessation of exposure? Aquat Toxicol. 155:213-221.

Guilherme S, Santos MA, Gaivao I, Pacheco M. 2014b. DNA and chromosomal damage induced in fish (*Anguilla anguilla* l.) by aminomethylphosphonic acid (ampa)-the major environmental breakdown product of glyphosate. Environ Sci Pollut Res Int. 21:8730-8739.

Kier, LD. 2015. Review of genotoxicity biomonitoring studies of glyphosate-based formulations. Crit Rev Toxicol. 45(3):209-218.

Li AP, Long TJ. 1988. An evaluation of the genotoxic potential of glyphosate. Fundam Appl Toxicol. 10:537-546.

Li Q, Lambrechts MJ, Zhang Q, Liu S, Ge D, Yin R, Xi M, You Z. 2013. Glyphosate and ampa inhibit cancer cell growth through inhibiting intracellular glycine synthesis. Drug Des Devel Ther. 7:635-643.

Marques A, Guilherme S, Gaivao I, Santos MA, Pacheco M. 2014a. Erratum to: "Progression of DNA damage induced by a glyphosate-based herbicide in fish (*Anguilla anguilla*) upon exposure and post-exposure periods - insights into the mechanisms of genotoxicity and DNA repair". Comp Biochem and Physiol C Toxicol Pharmacol. 168C:1. doi: 10.1016/j.cbpc.2014.10.008.

Marques A, Guilherme S, Gaivao I, Santos MA, Pacheco M. 2014b. Progression of DNA damage induced by a glyphosate-based herbicide in fish (*Anguilla anguilla*) upon exposure and post-exposure periods - insights into the mechanisms of genotoxicity and DNA repair. Comp Biochem and Physiol C Toxicol Pharmacol. 166:126-133.

Menkes DB, Temple WA, Edwards IR. 1991. Intentional self-poisoning with glyphosate-containing herbicides. Hum Exp Toxicol. 10:103-107.

Moller P. 2005. Genotoxicity of environmental agents assessed by the alkaline comet assay. Basic Clin Pharmacol Toxicol. 96(Suppl. 1):1-42.

Paz-y-Miño C, Muñoz MJ, Maldonado A, Valladares C, Cumbal N, Herrera C, Robles P, Sánchez ME, López-Cortés A. 2011. Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border. Rev Environ Health. 26:45-51.

Genotoxicity Studies on Monsanto Glyphosate Formulations

Ames/Salmonella Mutagenicity Assay of MON 2139 (ROUNDUP®Herbicide Formulation). Kier, L.D., Stegeman, S.D., Costello, J.G., Schermes, S. MSL-11729; EHL91183/ML-91-440. February 7, 1992.

Mouse Micronucleus Study of ROUNDUP®Herbicide Formulation. Kier, L.D., Flowers, L.J., Huffman, M.B. EHL 91200/91204; /ML-91-434/ML-91-437. February 25, 1992.

MON 8709 Teste de Mutacao Genica Reversa (Teste de Ames). Renata Cristina Viana Silvino. RL81984AM; 19700/2010 – 16.0AM. August 8, 2011.

MON 8709 Teste do Micronucleo em Medula Ossea de Camundongo. Flavia Thomazotti Calaro. RL81985MN; 19700/2010 – 17.0MN.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 14420 (Teste de Ames). Marise Ferro Carvalho Marques. RF-G11.19/99. 12/01/ 2000.

Estudo do Micronucleo em Medula Ossea de Camundongo para MON 14420. Marise Ferro Carvalho Marques. RF-G12.36/99. 01/09/1999.

Ames/Salmonella Mutagenicity Assay of MON 14445 DIRECT®Herbicide Formulation). Kier, L.D., Stegeman, S.D., Costello, J.G., Schermes, S. MSL – 11731; EHL 91185/ML-91-442. February 7, 1992.

Mouse Micronucleus Study of DIREC ®Herbicide Formulation. Kier, L.D., Flowers, L.J., Huffman, M.B. EHL 91202/91206; /ML-91-436/ML-91-439. February 25, 1992.

The Salmonella typhimurium reverse mutation by ROUNDUP WG. BioAgri Report # G.1.1 – 011/98. April 02, 1998.

A micronucleus study in mice for ROUNDUP WG. BioAgri Report # G.1.2 – 59/97. August 22, 1998.

Bacterial Reverse Mutation Assay with a Confirmatory Assay. MON 76313. Michael Mecchi. Covance Study Number 6103-757; Monsanto Study Number CV-08-242. 24 November 2008.

In Vivo Mouse Bone Marrow Micronucleus Assay. MON 76313. Yong Xu. Covance Study Number 6103-758; Monsanto Study Number CV-08-243. 03 December 2008.

MON 76313 Teste de Mutacao Genica Reversa (Teste de Ames). Renata Cristina Viana Silvino. RL108867AM; 11241/2011 – 5.0AM. March 1, 2012.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 77063. Marise Ferro Carvalho Marques. RF-G11.59/98. 12/07/ 1999.

Teste de Micronucleo em para MON 77063 em camundongos. Marise Ferro Carvalho Marques. RF-G12.16/99. May 7, 1999.

The Salmonella typhimurium reverse mutation by MON 77280. BioAgri Report # G.1.1 – 046/97. March 05, 1998.

A micronucleus study in mice for MON 77280. BioAgri Report # G.1.2 – 48/97. February 20, 1998.

MON 77280 Bacterial Reverse Mutation Test (Ames Test). Mara Rubia Camolesi. RL42517AM-B; 12208/2009 – 3.0AM.

MON 77280 Teste de Mutacao Genica Reversa em *Salmonella typhimurium* (Teste de Ames). Mara Rubia Camolesi. RL42517AM; 12208/2009 – 3.0AM. April 8, 2010.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 77391. Marise Ferro Carvalho Marques. RF-G11.60/98. 15/07/ 1999.

Teste de Micronucleo em para MON 77391 em camundongos. Marise Ferro Carvalho Marques. RF-G12.17/99. May 11, 1999.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 78036. Valeria C. Franco Perina. RF-G11.62/98. 12 November 1999.

Teste de Micronucleo para MON 78036 em camundongos. Marise Ferro Carvalho Marques. RF-G12.19/99. 12 May 1999.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 78091 (Teste de Ames). Marise Ferro Carvalho Marques. RF-G11.18/99. 12/01/2000.

Estudo do Micronucleo em Medula Ossea de Camundongos para MON 78091. Marise Ferro Carvalho Marques. RF-G12.35/99. 01/09/1999.

Mutacao Genica Reversa em *Salmonella typhimurium* para MON 78128 (Teste de Ames). Marise Ferro Carvalho Marques. RF-G11.42/99. 25/10/1999.

Estudo do Micronucleo em Medula Ossea de Camundongos para MON 78128. Marise Ferro Carvalho Marques. RF-G12.64/99. 25/11/1999.

MON 78239: *Salmonella – Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with Confirmatory Assay. Michael Mecchi. Covance Study Number 6103-355; Monsanto Study Number CV-2002-186. April 16, 2003.

In Vivo Mouse Bone Marrow Micronucleus Assay with MON 78239. Gregory Erexson. Covance Study Number 6103-352; Monsanto Study Number CV-2002-187. 24 April 2003.

MON 78634: *Salmonella – Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with Confirmatory Assay. Michael Mecchi. Covance Study Number 6103-354; Monsanto Study Number CV-2002-188. April 16, 2003.

In Vivo Mouse Bone Marrow Micronucleus Assay with MON 78634. Gregory Erexson. Covance Study Number 6103-353; Monsanto Study Number CV-2002-189. 24 April 2003.

Salmonella – Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with MON 78910. Yong Xu. Covance Study Number 6103-511; Monsanto Study Number CV-2005-119. 01 March 2006.

In Vivo Mouse Bone Marrow Micronucleus Assay. MON 78910. Gregory Erexson. Covance Study Number 6103-512; Monsanto Study Number CV-2005-120. 01 March 2006.

Bacterial Reverse Mutation Assay with a Confirmatory Assay. MON 79864. Michael Mecchi. Covance Study Number 6103-745; Monsanto Study Number CV-08-030. 09 September 2008.

In Vivo Mouse Bone Marrow Micronucleus Assay. MON 79864. Yong Xu. Covance Study Number 6103-746; Monsanto Study Number CV-08-031. 07 October 2008; Amended 03 March 2011.

Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay. MON 79991. Michael Mecchi. Covance Study Number 6103-709; Monsanto Study Number CV-2007-082. 30 January 2009.

In Vivo Mouse Bone Marrow Micronucleus Assay with MON 79991. Yong Xu. Covance Study Number 6103-708; Monsanto Study Number CV-2007-083. 23 January 2009.

To: Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Nguyen, Khue[Nguyen.Khue@epa.gov]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]; HEERING, DAVID C [AG/1000][david.c.heering@monsanto.com]; HEYDENS, WILLIAM F [AG/1000][william.f.heydens@monsanto.com]; NYANGULU, JAMES M [AG/1920][james.m.nyangulu@monsanto.com]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Lowit, Anna[Lowit.Anna@epa.gov]; Perron, Monique[Perron.Monique@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Bloem, Thomas[Bloem.Thomas@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Tue 4/19/2016 5:36:37 PM
Subject: RE: notes from April 5 glyphosate meeting

All:

We are not aware of any additional similar data submitted to Health Canada and not EPA.

Thank you,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Moriarty, Thomas [mailto:Moriarty.Thomas@epa.gov]
Sent: Monday, April 18, 2016 8:39 AM
To: JENKINS, DANIEL J [AG/1920]; Nguyen, Khue; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: RE: notes from April 5 glyphosate meeting

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Thank you for this, we'll be in touch,

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Monday, April 18, 2016 8:28 AM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>; LISTELLO, JENNIFER J [AG/1000] <jennifer.j.listello@monsanto.com>; HEERING, DAVID C [AG/1000] <david.c.heering@monsanto.com>; HEYDENS, WILLIAM F [AG/1000] <william.f.heydens@monsanto.com>; NYANGULU, JAMES M [AG/1920] <james.m.nyangulu@monsanto.com>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Moriarty, Thomas <Moriarty.Thomas@epa.gov>; Smith, Charles <Smith.Charles@epa.gov>; Lowit, Anna <Lowit.Anna@epa.gov>; Perron, Monique <Perron.Monique@epa.gov>; Dunbar, Anwar <Dunbar.Anwar@epa.gov>; Bloem, Thomas <Bloem.Thomas@epa.gov>
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*1: Final Addendum to the renewal assessment report on glyphosate, compiled by EFSA, October 2015. http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302

*2: EFSA explains the carcinogenicity assessment of glyphosate: http://www.efsa.europa.eu/sites/default/files/4302_glyphosate_complementary.pdf

Thanks and please let us know if you have any questions.

Best Regards,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East

Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Wednesday, April 06, 2016 2:57 PM
To: JENKINS, DANIEL J [AG/1920]; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Moriarty, Thomas; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: notes from April 5 glyphosate meeting

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Thanks again for being so responsive to our request for information.

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

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To: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]; Nguyen, Khue[Nguyen.Khue@epa.gov]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]; HEERING, DAVID C [AG/1000][david.c.heering@monsanto.com]; HEYDENS, WILLIAM F [AG/1000][william.f.heydens@monsanto.com]; NYANGULU, JAMES M [AG/1920][james.m.nyangulu@monsanto.com]
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From: Moriarty, Thomas
Sent: Mon 4/18/2016 12:38:40 PM
Subject: RE: notes from April 5 glyphosate meeting

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To: Nguyen, Khue <Nguyen.Khue@epa.gov>; LISTELLO, JENNIFER J [AG/1000] <jennifer.j.listello@monsanto.com>; HEERING, DAVID C [AG/1000] <david.c.heering@monsanto.com>; HEYDENS, WILLIAM F [AG/1000] <william.f.heydens@monsanto.com>; NYANGULU, JAMES M [AG/1920] <james.m.nyangulu@monsanto.com>
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Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Wednesday, April 06, 2016 2:57 PM
To: JENKINS, DANIEL J [AG/1920]; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Moriarty, Thomas; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
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Risk Management and Implementation Branch 1

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From: JENKINS, DANIEL J [AG/1920]
Sent: Mon 4/18/2016 12:27:46 PM
Subject: RE: notes from April 5 glyphosate meeting
glyphosate monsanto meeting notes after team comments 4 6 16 MON suggest....docx
Tox Studies submitted to BfR for EU Annex 1 Renewal.pdf

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Glyphosate: 4/5/16 meeting between EPA and Monsanto—notes

EPA met with Monsanto to discuss EPA's recent information request for glyphosate. In an email dated 3/21/16, EPA requested information on the inert ingredients used in popular US and European formulations of glyphosate in the present day and also dating back to the 80s. EPA was particularly interested in information on how glyphosate formulations have changed over time in the last 20-30 years. In its email request, EPA included a list of 6 epi studies that were completed in the mid-1980s to the early 2000s; these studies were cited in the IARC's recent report on glyphosate. EPA included this list of studies because it was interested in characterizing potential differences in US and European glyphosate epidemiology studies.

Monsanto briefly discussed the epi studies that were referenced in EPA's 3/21/16 email and discussed why they are not suitable to assess carcinogenicity of glyphosate. Monsanto also briefly discussed glyphosate's history of safety and the conclusions of various regulatory agencies all over the world, many of which conclude that glyphosate was not carcinogenic.

EPA stated that at this time it was not interested in discussing the opinions of other regulatory agencies nor was it interested in debating glyphosate's alleged carcinogenicity at the April 5 meeting. Rather, EPA stated that it was in the midst of a large scale holistic review of the glyphosate database. EPA's approach for registration review risk assessment is to take a systematic and scientific, weight of the evidence approach, and would not rely on the regulatory conclusions of other regulatory agencies. In an effort to resolve questions about the potential toxicity of glyphosate, glyphosate formulations, and any co-formulants (inert ingredients and surfactants), EPA was interested in any data or information Monsanto may have on how the formulations may differ from data on the active ingredient and surfactants independently of one another.

Of particular interest to EPA are the following:

1) Toxicity (particularly repeat dose data) or pharmacokinetic formulation studies.
2) Information on the pharmacokinetics of glyphosate, including info on tissue dosimetry or metabolism.
3) *In vitro* studies on bioactivity (including cellular-based bioactivity).
4) Any *in vitro* ADME (absorption, distribution, metabolism, and excretion) studies
5) Any remaining carcinogenicity studies on glyphosate not yet submitted to EPA. At some point in the future, the agency may be interested in other toxicities (*e.g.*, developmental or reproductive toxicity).

EPA requested that rather than sending to the agency all the studies that might be relevant, Monsanto should start with a bibliography that EPA can use to compare with its own bibliography. The agency requested that Monsanto include data generated for both North American registrations as well as European registrations. Then EPA would be able to indicate which of these studies would be of potential use in its analysis and make a request for them. EPA indicated that this should be done as soon as possible.

There was also some discussion about changes in Monsanto's Roundup formulation over the years. Monsanto indicated that up until 2000, nearly all glyphosate products on the market were its Roundup formulation which used some form of tallow amine as a surfactant. Afterwards, the properties of

surfactants used and the ratio of surfactant to active ingredient were changed in most formulations due to a need for increased ai loading. Current products vary geographically due to various reasons, some having to do with marketing. EPA suggested that Monsanto provide in writing any information that documents the changes of glyphosate formulations over time and across the globe.

The agency appreciates Monsanto's cooperation in its attempt to conduct a thorough and transparent science-driven analysis of the human health effects of glyphosate under registration review.

Tox Studies submitted to BfR for EU Annex 1 Renewal

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BVL registration number	Data protection claimed Y/N	Owner[5]
KIIA 5 KIIIA1 7 (OECD)	EFSA	2009	Reasoned opinion: Modification of the residue definition of Glyphosate in genetically modified maize grain and soybeans, and in products of animal origin EFSA Journal 2009; 7(9):1310 ! EFSA-Q-2009-00372 ASB2012-3480	N	---
KIIA 5 KIIIA1 7 (OECD)	EFSA	2012	Final review of the Séralini et al. (2012a) publication on a 2-year rodent feeding study with glyphosate formulations and GM maize NK603 as published online on 19 September 2012 in Food and Chemical Toxicology *EFSA Journal 2012;10(11):2986* ASB2012-15513	N	---
KIIA 5 KIIIA1 7 (OECD)	European Commission	2002	Review report for the active substance glyphosate. Finalised in the Standing Committee on Plant Health at its meeting on 29 June 2001in view of the inclusion of glyphosate in Annex I of Directive 91/414/EEC. Glyphosat 6511/VI/99-final ASB2009-4191	N	---
KIIA 5 KIIIA1 7 (OECD)	Germany	1998	Glyphosate (Monograph) ASB2010-10302	N	---
KIIA 5 KIIIA1 7 (OECD)	Germany	1998	Glyphosate-trimesium (Monograph), ASB2010-10493	N	---
KIIA 5 KIIIA1 7 (OECD)	Germany	2000	Glyphosate (Monograph): Addendum B.6, ASB2013-2748	N	---
KIIA 5 KIIIA1 7 (OECD)	OECD	2002	OECD; Guidance Notes for Analysis and Evaluation of Chronic Toxicity and Carcinogenicity Studies ENV/JM/MONO(2002)19 ASB2013-3754	N	---

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KIIA 5 KIIIA1 7 (OECD)	Anonymous	2006	Backgrounder Response to “Glyphosate Toxic & Roundup Worse”. Monsanto statement. http://www.monsanto.com/products/Documents/glyphosate-background-materials/Response_ISIS_apr_06.pdf ASB2013-5455	N	---
KIIA 5.1 K IIA 5.6 (OECD	Antoniou M, Habib MEEM, Howard CV, Jennings RC, Leifert C, Nodari RO, C Robinson, Fagan J.	2011	Roundup and birth defects: Is the public being kept in the dark? Earth Open Source report. Available from: http://www.earthopensource.org/files/pdfs/Roundup-and-birth-defects/RoundupandBirthDefectsv5.pdf ASB2011-7202	N	---
KIIA 5.1 KIIA 5.10 (OECD)	Carr, K.H., Bleeke, M.S.	2012	Process Description for Identification, Review, and Categorization of Scientific Literature Concerning Glyphosate and AMPA Side-Effects on Health, the Environment, and Non-Target Species k.A. GLP: N, published: Y 2309656 / ASB2012-11583	N	LIT
KIIA 5.1 KIIA 5.10 (OECD)	Klimisch, H.J., Andreae, M., Tillmann, U.	1997	A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data Regulatory Toxicology and Pharmacology 25, 1-5 GLP: N, published: Y 2309856 / ASB2010-14388	N	LIT
KIIA 5.1.1 KIIA 5.5.3 KIIA 5.9 KIIA 5.10 KIIIA1 7.6.4 (OECD)	Acquavella, J.F., Alexander, B.H., Mandel, J.S., Gustin, C., Baker, B., Chapman, P., Bleeke, M.	2004	Glyphosate biomonitoring for farmers and their families: Results from the farm family exposure study Environmental Health Perspectives 112, 321-326 GLP: N, published: Y 2309536 / ASB2012-11528	N	LIT
KIIA 5.1.1 KIIA 5.4.4 KIIA 5.7.4 KIIA 5.10 (OECD)	Anadon, A., Martinez-Larranaga, M.R., Martinez, M.A., Castellano, V.J., Martinez, M., Martin, M.T., Nozal, M.J., Bernal, J.L.	2009	Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats Toxicol Lett 190, 91-95 GLP: N, published: Y 2309568 / ASB2012-11542	N	LIT

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KIIA 5.1.1 (OECD)	Blech, S.; Stratmann, A.	1995	Glyphosate: ADME-study in rats - Final report A&M 038/94, TOX9552251	N	---
KIIA 5.1.1 KIIA 5.4.4 (OECD)	Brewster, D. W.; Warren, J.; Hopkins, W. E.	1991	Metabolism of glyphosate in Sprague-Dawley rats: Tissue distribution, identification, and quantitation of glyphosate-derived materials following a single oral dose, Fundamental and Applied Toxicology 17(1991): 43-51 TOX9551791	N	---
KIIA 5.1.1 KIIA 5.3.2 KIIA 5.4 KIIA 5.5 KIIA 5.10 (OECD)	Chan, P. C.; Mahler, J. F.	1992	NTP technical report on toxicity studies of Glyphosate administered in dosed feed to F344/N rats and B6C3F1 mice, National Institutes of Health 16(1992) 1-57 TOX9551954	N	---
KIIA 5.1.1 (OECD)	Colvin, L. B.; Miller, J. A.	1973	Final report on CP 67573 residue and metabolism. Part 9: The gross distribution of n-phosphonomethylglycine-^{14}C in the rabbit TOX9552353	N	---
KIIA 5.1.1 (OECD)	Colvin, L. B.; Miller, J. A..	1973	CP 67573 residue and metabolism. Part 13: The dynamics of accumulation and depletion of orally ingested N-phosphonomethylglycine-^{14}C TOX9552355	N	---
KIIA 5.1.1 (OECD)	Davies, D.J.	1996	Glyphosate acid: Excretion and tissue retention of a single oral dose (10 mg/kg) in the rat CTL/4940 SYN GLP: Y, published: N 2309074 / TOX2000-1977	N	SYN
KIIA 5.1.1 (OECD)	Davies, D.J.	1996	Glyphosate acid: Excretion and tissue retention of a single oral dose (1000 mg/kg) in the rat CTL/4942 SYN GLP: Y, published: N 2309076 / TOX2000-1978	N	SYN
KIIA 5.1.1 KIIA 5.1.3 (OECD)	Davies, D. J.	1996	Glyphosate acid: Excretion and Tissue Retention of a Single Oral Dose (10 mg/kg) in the Rat Following Repeat Dosing CTL/P/4944 SYN GLP: Y, published: N 2309078 / TOX2000-1979	N	SYN
KIIA 5.1.1 KIIA 5.1.3 (OECD)	Davies, D. J.	1996	Glyphosate acid: Whole body autoradiography in the rat (10 mg/kg) CTL/P/4943 SYN GLP: Y, published: N 2309080 / TOX2000-1980	N	SYN

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KIIA 5.1.1 KIIA 5.9 KIIA 5.10 (OECD)	Hoppe, H.-W.	2013	Glyphosate and AMPA: Determination of glyphosate residues in human urine samples from 18 European countries Medical Laboratory Bremen, MLHB-2013-06-06 ASB2013-8037	N	---
KIIA 5.1.1 (OECD)	Howe, R. K.; Chott, R. C.; McClanahan, R. H.	1988	The metabolism of glyphosate in Sprague/Dawley rats. Part II. Identification, characterization, and quantitation of glyphosate and its metabolites after intravenous and oral administration, MSL-7206 ! 206300, TOX9552357	N	---
KIIA 5.1.1 (OECD)	Knowles, S.L.; Mookherjee, C.R.	1996	[^{14}C]-glyphosate: Absorption, distribution, metabolism and excretion following oral administration to the rat 1413/2-1011 NUF GLP: Y, published: N 2309072 / ASB2012-11380	Y	NUF
KIIA 5.1.1 (OECD)	Leuschner, J.	1995	Metabolism study of ^{14}C-labelled glyphosate after single oral and intravenous administration to Sprague-Dawley rats, 9202/95 TOX9650071	N	---
KIIA 5.1.1 KIIA 5.1.3 (OECD)	Macpherson, D.	1996	Glyphosate acid: Biotransformation in the rat CTL/P/5058 SYN GLP: Y, published: N 2309082 / TOX2000-1981	N	SYN
KIIA 5.1.1 KIIA 5.10 (OECD)	Mage, D.T.	2006	Suggested corrections to the Farm Family Exposure Study Environmental Health Perspectives 114, A633-A634 GLP: N, published: Y 2309900 / ASB2012-11888	N	LIT
KIIA 5.1.1 (OECD)	McEwen, A.B.	1995	HR-001: Metabolism in the rat SNY 332/951256 HLS GLP: Y, published: N 2309070 / ASB2012-11379	N	ALS
KIIA 5.1.1 (OECD)	Powles, P.; Hopkins, R.	1992	(^{14}C)-glyphosate: Absorption and distribution in the rat - preliminary study TOX9552358	N	---
KIIA 5.1.1 (OECD)	Powles, P.; Hopkins, R.	1992	(^{14}C)-glyphosate: Absorption, distribution, metabolism and excretion in the rat, TOX9300343	N	---

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KIIA 5.1.1 (OECD)	Ridley, W.P.; Mirly, K.	1988	The metabolism of glyphosate in Sprague/Dawley rats. I. Excretion and tissue distribution of Glyphosate and its metabolites following intravenous and oral administration MSL-7215 ! EHL 86139 ! ML-86-438 TOX9552356	N	---
KIIA 5.2.1 (OECD)	Arcelin, G.	2007	Glyphosate technical material: Acute oral toxicity study in rats (Up and Down procedure) B02755; T007035-05 SYN GLP: Y, published: N 2309111 / ASB2012-11391	Y	SYN
KIIA 5.2.1 (OECD)	Branch, D. K.	1981	Acute oral toxicity of MON 0139 to rats 800257 ! ML-80-261 TOX9552321	N	---
KIIA 5.2.1 (OECD)	Brett, M. G	1990	Acute oral toxicity in the rat: Glyphosate technical R231 ! AGC-900823B ! AGC-101 TOX9500261	N	---
KIIA 5.2.1 (OECD)	Brown, J. C.; Ogilvie, S. W.	1995	Glyphosate technical 95 %: Acute oral toxicity (LD_{50}) test in rat 10670 ! IRI 556073 TOX9500377	N	---
KIIA 5.2.1 (OECD)	Cuthbert, J. A.; Jackson, D.	1989	Glyphosate technical: Acute oral toxicity (limit) test in rats 5883 ! IRI 243268 TOX9552319	N	---
KIIA 5.2.1 (OECD)	Dideriksen, L. H.; Skydsgaard, K.	1991	Assessment of acute oral toxicity of "Glyphosate technical" to mice - incl. Addendum 12321 TOX9552320	N	---
KIIA 5.2.1 (OECD)	Do Amaral Guimaraes, S.P.	2008	Acute Oral Toxicity Study in Wistar Hannover Rats for Glyphosate Technical RF -3996.305.475.07 HAG GLP: Y, published: N 2309100 / ASB2012-11389	Y	HAG
KIIA 5.2.1 (OECD)	Doyle, C.E.	1996	Glyphosate Acid: Acute Oral Toxicity Study in Rats CTL/P/4660 SYN GLP: Y, published: N 2309109 / TOX2000-1982	N	SYN
KIIA 5.2.1 (OECD)	Dreher, D. M.	1994	Glyphosate premix: Acute oral toxicity (limit test) in the rat 545/37 TOX9552322	N	---

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KIIA 5.2.1 (OECD)	Enami, T., Nakamura, H.	1995	Acute Toxicity Study of MON 0139 By Oral Administration in Mice XX-95-205 MON GLP: Y, published: N 2309115 / ASB2012-11393	Y	MON
KIIA 5.2.1 (OECD)	Haferkorn, J.	2009	Acute Oral Toxicity Study of Glyphosate TC in Rats 23910 HAG GLP: Y, published: N 2309092 / ASB2012-11385	Y	HAG
KIIA 5.2.1 (OECD)	Haferkorn, J.	2010	Acute Oral Toxicity Study of Glyphosate TC in Rats 24874 HAG GLP: Y, published: N 2309094 / ASB2012-11386	Y	HAG
KIIA 5.2.1 (OECD)	Haferkorn, J.	2010	Acute Oral Toxicity Study of Glyphosate TC in Rats 24602 HAG GLP: Y, published: N 2309096 / ASB2012-11387	Y	HAG
KIIA 5.2.1 (OECD)	Heenehan, P.R., Braun, W.G. and Rinehart, W.E.	1979	Acute Oral Toxicity Study in Rats. BD-77-428 MON GLP: N, published: N 2309107 / Z35541	N	MON
KIIA 5.2.1 (OECD)	Komura, Hitoshi	1995	HR-001: Acute Oral Toxicity Study In Rats IET 94-0134 ALS GLP: Y, published: N 2309086 / ASB2012-11382	Y	ALS
KIIA 5.2.1 (OECD)	Komura, Hitoshi	1995	HR-001: Acute Oral Toxicity Study In Mice IET 94-0133 ALS GLP: Y, published: N 2309088 / ASB2012-11383	Y	ALS
KIIA 5.2.1 (OECD)	Merkel, D.	2005	Glyphosate Acid Technical - Acute Oral Toxicity Up and Down Procedure in Rats PSL 15274 HAG GLP: Y, published: N 2309098 / ASB2012-11388	Y	HAG
KIIA 5.2.1 (OECD)	Moore, G.E.	1999	NUP5a99 62 % glyphosate MUP: Acute oral toxicity study in rats - Limit test 7907 NUF GLP: Y, published: N 2309117 / ASB2012-11394	Y	NUF

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KIIA 5.2.1 (OECD)	Pooles, A.	2014	Glyphosate: Acute oral toxicity in the rat - fixed dose method Report No.: 41401853, Harlan Laboratories Ltd., Derbyshire, DE72 2GD, UK Date: 2014-00-01, not published ASB2014-9147	Y	
KIIA 5.2.1 (OECD)	Reagan, E. L.	1987	Acute oral LD_{50} study of MON-8750 in Sprague-Dawley rats FDRL 9308A TOX9552323	N	---
KIIA 5.2.1 (OECD)	Reagan, E. L.	1987	Acute oral toxicity of MON 8750 in Sprague-Dawley rats FD-86-431/9308A Z85869	N	---
KIIA 5.2.1 (OECD)	Reagan, E.L. and Laveglia, J.	1988	Acute Oral Toxicity Study of Glyphosate Batch/lot/nbr no. XLI-55 in Sprague/Dawley rats FD-88-29 (FDRL 88.20 MON 88.2053.007) GLP: Y, published: N 2309105 / Z35389	N	MON
KIIA 5.2.1 (OECD)	Sharp, V. M.	1995	Final report for oral and dermal LD_{50} tests with Sanachem glyphosate acid technical in rats, limit test 00917 TOX9650909	N	---
KIIA 5.2.1 KIIA 5.2.2 (OECD)	Sharp, V. M.	1995	Final report for oral and dermal LD_{50} tests with Sanachem glyphosate 62 % IPA in rats, limit test 00926 TOX9650910	N	---
KIIA 5.2.1 (OECD)	Simon, C.	2009	Glyphosate Technical: Acute oral Toxicity Study in Rat, C22864, C22864 EXC GLP: Y, published: N 2309090 / ASB2012-11384	Y	EXC
KIIA 5.2.1 (OECD)	Snell, K.	1994	Glyphosate: Acute oral toxicity (limit test) in the rat 710/14 TOX9500245	N	---
KIIA 5.2.1 (OECD)	Suresh, T. P.	1991	Acute oral toxicity study with glyphosate technical (FSG 03090 H/05 march 90) in Wistar rats ES.874.AOR ! ES-GPT-AOR ! TOXI-874/1990 TOX9551088	N	---

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KIIA 5.2.1 (OECD)	Suresh, T. P.	1991	Acute oral toxicity study with glyphosate technical (FSG 03090 H/05 march 90) in swiss albino mice ES.875.AOM ! ES-GPT-AOM ! TOXI-875/1990 TOX9551089	N	---
KIIA 5.2.1 (OECD)	Talvioja, K.	2007	GLYPHOSATE TECHNICAL (NUP05068) : Acute oral toxicity study in rats BO2272 NUF GLP: Y, published: N 2309103 / ASB2012-11390	Y	NUF
KIIA 5.2.1 (OECD)	Tavaszi, J.	2011	Glyphosate technical - Acute Oral Toxicity Study in the Rat (Up and Down Procedure) 10/218-001P SYN GLP: Y, published: N 2309113 / ASB2012-11392	Y	SYN
KIIA 5.2.1 (OECD)	Tornai, A.; Rozsnyoi, F. Turczer, K. Arszenovitz, S. Dufner, A.	1994	Glyphosate (Alkaloida, Tiszavasvari): Acute oral toxicity in rats GHA-94-401/R TOX9650142	N	---
KIIA 5.2.1 (OECD)	Tos, E. G.; Maraschin, R.; Orlando, L.	1994	Glyphosate technical: Acute oral toxicity study in mice 940020 ! PRO629 TOX9551624	N	---
KIIA 5.2.1 (OECD)	Ullmann, L.; Sacher, R.; Janiak, T.; Vogel, O.	1989	Acute oral toxicity study with glyphosate technical (isopropylamine salt 62 % in water equivalent to 46 % of N-phosphonomethylglycine acid) in rats 238050 ! PRO439 TOX9551623	N	---
KIIA 5.2.1 (OECD)	Walker, D. J.; Jones, J. R.	1992	Glyphosate technical: Acute oral toxicity (limit test) in the rat 134/37 TOX9551810	N	---
KIIA 5.2.1 (OECD)	Wang, S. C.	1987	Acute oral toxicity of 41 % SN750721 solution in mice - Test report entrusted by Shinung Corporation TX58AO2 TOX9500376	N	---
KIIA 5.2.1 (OECD)	Wang, S.-C.	1987	Acute oral toxicity of 64 % SN750721 technical liquid in mice Test report entrusted by Shinung Corporation TX58AO1 TOX9500375	N	---

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KIIA 5.2.1 (OECD)	You, J.	2009	Glyphosate: Acute Oral Toxicity Study (UDP) In Rats 12170-08 HEL GLP: Y, published: N 2309084 / ASB2012-11381	Y	HAG
KIIA 5.2.2 (OECD)	Arcelin, G.	2007	Glyphosate technical material: Acute dermal toxicity study in rats B02766 (T007036-05) SYN GLP: Y, published: N 2309141 / ASB2012-11404	Y	SYN
KIIA 5.2.2 (OECD)	Branch, D. K.	1981	Acute dermal toxicity of MON 0139 to rabbits 800258 ! ML-80-261 TOX9552326	N	---
KIIA 5.2.2 (OECD)	Brett, M. G.	1990	Acute dermal toxicity study in the rat: Glypho-sate technical AGC-900823A ! AGC-301 ! R232 TOX9551793	N	---
KIIA 5.2.2 (OECD)	Busch, B.	1987	Acute dermal toxicity study of Mon 8750 in New Zealand white rabbits FDRL 9308A ! FD-86-431 TOX9552327	N	---
KIIA 5.2.2 (OECD)	Busch, B.	1987	Acute dermal toxicity study of Mon 8722 in New Zealand white rabbits FDRL 9307A ! FD-86-430 TOX9552328	N	---
KIIA 5.2.2 (OECD)	Cuthbert, J.A., Jackson, D.	1989	Glyphosate Technical Acute Dermal Toxicity (Limit) Test in Rats 5884 CHE GLP: Y, published: N 2309119 / TOX9300328	N	CHE
KIIA 5.2.2 (OECD)	Do Amaral Guimaraes, S.P.	2008	Acute Dermal Toxicity in Wistar Hannover Rats for Glyphosate Technical RF-3996.310.456.07 HAG GLP: Y, published: N 2309135 / ASB2012-11402	Y	HAG
KIIA 5.2.2 (OECD)	Doyle, C.E.	1996	Glyphosate Acid: Acute Dermal Toxicity in the Rat CTL/P/4664 SYN GLP: Y, published: N 2309139 / TOX2000-1983	Y	SYN
KIIA 5.2.2 (OECD)	Haferkorn, J.	2009	Acute Dermal Toxicity Study of Glyphosate TC in CD Rats LPT 23912 HAG GLP: Y, published: N 2309127 / ASB2012-11398	Y	HAG

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KIIA 5.2.2 (OECD)	Haferkorn, J.	2010	Acute Dermal Toxicity Study of Glyphosate TC in CD Rats LPT 24876 HAG GLP: Y, published: N 2309129 / ASB2012-11399	Y	HAG
KIIA 5.2.2 (OECD)	Haferkorn, J.	2010	Acute Dermal Toxicity Study of Glyphosate TC in CD Rats LPT 24604 HAG GLP: Y, published: N 2309131 / ASB2012-11400	Y	HAG
KIIA 5.2.2 (OECD)	Komura, Hitoshi	1995	HR-001: Acute dermal toxicity study in rats IET 94-0154 ALS GLP: Y, published: N 2309123 / ASB2012-11396	N	ALS
KIIA 5.2.2 (OECD)	Merkel, D.	2005	Glyphosate Acid Technical: Acute Dermal Toxicity Study in Rats - Limit Test PSL 15275 HAG GLP: Y, published: N 2309133 / ASB2012-11401	Y	HAG
KIIA 5.2.2 (OECD)	Meyer-Carrive, I.; Bolt, A. G.	1994	Acute dermal toxicity of glyphosate technical in the rat T1586.3.A TOX9500378	N	---
KIIA 5.2.2 (OECD)	Reagan, E. L.; Laveglia, J.	1988	Acute dermal toxicity of glyphosate Batch/lot/nbr no. XLI-55 in new zealand white rabbits 88.2053.008 ! FD-88-29 TOX9552325	N	---
KIIA 5.2.2 (OECD)	Simon, C.	2009	Glyphosate Technical: Acute Dermal Toxicity Study in Rat C22875 EXC GLP: Y, published: N 2309125 / ASB2012-11397	Y	EXC
KIIA 5.2.2 (OECD)	Snell, K.	1994	Glyphosate: Acute dermal toxicity (limit test) in the rat 710/15 TOX9500246	N	---
KIIA 5.2.2 (OECD)	Suresh, T. P.	1991	Acute dermal toxicity study with glyphosate technical (FSG 03090 H/05 march 90) in Wistar rats ES.876.ADR ! ES-GPT-ARD ! TOXI-876/1990 TOX9551090	N	---

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KIIA 5.2.2 (OECD)	Talvioja, K.	2007	GLYPHOSATE TECHNICAL (NUP05068): Acute dermal toxicity study in rats B02283 NUF GLP: Y, published: N 2309137 / ASB2012-11403	Y	NUF
KIIA 5.2.2 (OECD)	Tornai, A.; Rozsnyoi, F. Turczer, K. Arszenovitz, S. Dufner,A.	1994	Glyphosate (Alkaloida, Tiszavasvari): Acute dermal toxicity in rats GHA-94-402/R TOX9650143	N	---
KIIA 5.2.2 (OECD)	Ullmann, L.; Sacher, R.; Janiak, T.; Vo-gel, O.	1989	Acute dermal toxicity study with glyphosate technical (isopropylamine salt 62 % in water equivalent to 46 % of N-phosphonomethylglycine acid) in rats 238061 ! PRO425 TOX9551625	N	---
KIIA 5.2.2 (OECD)	Walker, D. J.; Jones, J. R.	1992	Glyphosate technical: Acute dermal toxicity (limit test) in the rat 134/38 TOX9551813	N	---
KIIA 5.2.2 (OECD)	You, J.	2009	Glyphosate - Acute Dermal Toxicity Study in Rats 12171-08 HAG GLP: Y, published: N 2309121 / ASB2012-11395	Y	HAG
KIIA 5.2.2 (OECD)	Zelenak	2011	Glyphosate Technical - Acute Dermal Toxicity Study in Rats - Final Report Amendmend 1 10/218-002P SYN GLP: Y, published: N 2309143 / ASB2012-11405	Y	SYN
KIIA 5.2.3 (OECD)	Bechtel, C. L.	1988	Acute inhalation study of MON 8750 technical EHL 87147 ! ML-87-228 TOX9552332	N	---
KIIA 5.2.3 (OECD)	Blagden, S. M.	1994	Glyphosate premix: Acute inhalation toxicity study four-hour exposure (nose only) in the rat 523-001 ! 545/39 TOX9552331	N	---
KIIA 5.2.3 (OECD)	Blagden, S. M.	1995	Glyphosate: Acute inhalation toxicity study four-hour exposure (nose only) in the rat 710/16 TOX9500247	N	---
KIIA 5.2.3 (OECD)	Bonnette	2004	An acute nose-only inhalation toxicity study in rats with MON 78623 SB-2003-116 MON GLP: Y, published: N 2309169 / ASB2012-11417	Y	MON

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KIIA 5.2.3 (OECD)	Carter, L.	2009	Glyphosate - Acute Inhalation Toxicity Study in Rats 12107-08 HAG GLP: Y, published: N 2309155 / ASB2012-11411	Y	HAG
KIIA 5.2.3 (OECD)	Decker, U.	2007	Glyphosate technical (NUP05068) : 4-Hour acute inhalation toxicity study in rats B02327 NUF GLP: Y, published: N 2309161 / ASB2012-11414	Y	NUF
KIIA 5.2.3 (OECD)	Dudek, B. R.	1987	Acute toxicity of Rodeo herbicide administered by inhalation to male and female Sprague-Dawley rats EHL 86105 ! ML-86-281 ! MSL 6582 TOX9552330	N	---
KIIA 5.2.3 (OECD)	Griffith, D.R.	2009	Glyphosate Tech: Acute Inhalation Toxicity (Nose only) Study in the Rat 2743/0001 EXC GLP: Y, published: N 2309149 / ASB2012-11408	Y	EXC
KIIA 5.2.3 (OECD)	Haferkorn, J.	2009	Acute Inhalation Toxicity Study of Glyphosate TC in Rats LPT 23911 HAG GLP: Y, published: N 2309151 / ASB2012-11409	Y	HAG
KIIA 5.2.3 (OECD)	Haferkorn, J.	2010	Acute Inhalation Toxicity Study of Glyphosate TC In Rats 24603 HEL GLP: Y, published: N 2309145 / ASB2012-11406	Y	HAG
KIIA 5.2.3 (OECD)	Haferkorn, J.	2010	Acute Inhalation Toxicity Study of Glyphosate TC in Rats LPT 24875 HAG GLP: Y, published: N 2309153 / ASB2012-11410	Y	HAG
KIIA 5.2.3 (OECD)	Koichi, E.	1995	HR-001: Acute inhalation toxicity study in rats IET 94-0155 ALS GLP: Y, published: N 2309147 / ASB2012-11407	Y	ALS
KIIA 5.2.3 (OECD)	McDonald, P.; Anderson, B. T.	1989	Glyphosate technical: Acute inhalation toxicity study in rats (limit test) 5993 ! IRI 642062 TOX9552329	N	---

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KIIA 5.2.3 (OECD)	Merkel, D.	2005	Glyphosate Acid Technical: Acute Inhalation Toxicity Study in Rats - Limit Test PSL 15276 HAG GLP: Y, published: N 2309157 / ASB2012-11412	Y	HAG
KIIA 5.2.3 (OECD)	Nagy, K.	2011	Glyphosate Technical - Acute inhalation Toxicity Study (Nose-only) in the Rat 11/054-004P SYN GLP: Y, published: N 2309165 / ASB2012-11415	Y	SYN
KIIA 5.2.3 (OECD)	Rattray, N.J.	1996	Glyphosate Acid: 4-Hour Acute Inhalation Toxicity Study in the Rat CTL/P/4882 SYN GLP: Y, published: N 2309163 / TOX2000-1984	Y	SYN
KIIA 5.2.3 (OECD)	Thevenaz, P.; Biedermann, K.	1989	4-hour, acute inhalation toxicity study with glyphosate technical in rats 238105 ! PRO426 TOX9551626	N	---
KIIA 5.2.3 (OECD)	Tornai, A.; Kovacs, C.; Rozsnyoi, F. Turczer, K. Arszenovits, S. Dufner, A..	1994	Glyphosate (Alkaloida, Tiszavasvari): Acute inhalation toxicity in rats GHA-94-403/R TOX9650144	N	---
KIIA 5.2.3 (OECD)	Wnorowski, G.	1999	NUP5a99 62 % glyphosate MUP: Acute inhalation toxicity study in rats - Limit test 7909 NUF GLP: Y, published: N 2309167 / ASB2012-11416	Y	NUF
KIIA 5.2.4 (OECD)	Arcelin, G.	2007	Glyphosate technical material: Primary skin irritation study in rabbits (4-hour semi-occlusive application) B02777 (T007037-05) SYN GLP: Y, published: N 2309193 / ASB2012-11426	Y	SYN
KIIA 5.2.4 (OECD)	Brett, M. G.	1990	Acute dermal irritation/corrosion of glyphosate technical in the rabbit (intact and abraded skin) AGC-900822A ! AGC-001 ! R233 TOX9551794	N	---
KIIA 5.2.4 (OECD)	Busch, B.	1987	Primary dermal irritation study of Mon-8750 in New Zealand white rabbits FDRL 9308A ! FD-86-431 TOX9552336	N	---

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KIIA 5.2.4 (OECD)	Canabrava Frossard de Faria, B.C.F.	2008	Acute Dermal Irritation/Corrosion Study in Rabbits with Glyphosate Technical RF-3996.311.476.07 HAG GLP: Y, published: N 2309185 / ASB2012-11425	Y	HAG
KIIA 5.2.4 (OECD)	Cuthbert, J. A.; Jackson, D.	1989	Glyphosate technical: Primary skin irritation test in rabbits 5885 ! IRI 243268 TOX9552333	N	---
KIIA 5.2.4 (OECD)	Doyle, C.E.	1996	Glyphosate Acid: Skin Irritation To The Rabbit CTL/P/4695 SYN GLP: Y, published: N 2309191 / TOX2000-1985	Y	SYN
KIIA 5.2.4 (OECD)	Dreher, D. M.	1994	Glyphosate premix: Acute dermal irritation test in the rabbit 565-003 ! 545/40 TOX9552335	N	---
KIIA 5.2.4 (OECD)	Hideo, U.	1995	HR-001: Primary Dermal irritation study in rabbits IET 95-0035 ALS GLP: Y, published: N 2309175 / ASB2012-11420	Y	ALS
KIIA 5.2.4 (OECD)	Leuschner, J.	2009	Acute Dermal Irritation/Corrosion Test (Patch Test) of Glyphosate TC In Rabbits 24877 HEL GLP: Y, published: N 2309173 / ASB2012-11419	Y	HAG
KIIA 5.2.4 (OECD)	Leuschner, J.	2009	Acute Dermal Irritation/Corrosion Test (Patch Test) of Glyphosate TC in Rabbits LPT 23913 HAG GLP: Y, published: N 2309177 / ASB2012-11421	Y	HAG
KIIA 5.2.4 (OECD)	Leuschner, J.	2010	Acute Dermal Irritation/Corrosion Test (Patch Test) of Glyphosate TC in Rabbits LPT 24605 HAG GLP: Y, published: N 2309179 / ASB2012-11422	Y	HAG
KIIA 5.2.4 (OECD)	Merkel, D.	2005	Glyphosate Acid Technical - Primary Skin Irritation Study in Rabbits PSL 15278 HAG GLP: Y, published: N 2309183 / ASB2012-11424	Y	HAG

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KIIA 5.2.4 (OECD)	Reagan, E.L. & Laveglia, J.	1988	Primary Dermal Irritation Study of Glyphosate Batch/lot/nbr no. XLI-55 in New Zealand White Rabbits FD-88-29 (FDRL 88.20 MON GLP: Y, published: N 2309187 / Z35394	N	MON
KIIA 5.2.4 (OECD)	Snell, K.	1994	Glyphosate 360g/L: Acute dermal irritation test in the rabbit 710/29 TOX9500248	N	---
KIIA 5.2.4 (OECD)	Suresh, T. P.	1991	Primary skin irritation study with glyphosate technical (FSG 03090 H/05 march 90) in New Zealand white rabbits ES.878.SKIN ! TOXI-878/1990 ! ES-GPT-SKIN TOX9551092	N	---
KIIA 5.2.4 (OECD)	Talvioja, K.	2007	Glyphosate Technical (NUP 05068): Primary Skin Irritation Study in Rabbits (4-Hour Semi-Occlusive Application) B02294 NUF GLP: Y, published: N 2309171 / ASB2012-11418	Y	NUF
KIIA 5.2.4 (OECD)	Tornai, A.; Rozsnyoi, F.; Turczer, K. Arszenovits, S. Dufner,A.	1994	Glyphosate (Alkaloida, Tiszavasvari): Primary dermal irritation study in rabbits GHA-93-404/N TOX9650145	N	---
KIIA 5.2.4 (OECD)	Tos, E. G.; Maraschin, R.	1991	Acute dermal irritation study in New Zealand White rabbits treated with the test article glyphosate tecnico 98 % 910259 ! PRO495 TOX9551627	N	---
KIIA 5.2.4 (OECD)	Ullmann, L.; Porricello, T.; Janiak, T.	1989	Primary skin irritation study with glyphosate technical (isopropylamine salt 62 % in water equivalent to 46 % of N-phosphonomethylglycine acid) in rabbits (4-hour semi-occlusive application on intact and abraded skin) 238072 ! PRO438 TOX9551628	N	---
KIIA 5.2.4 (OECD)	You, J.	2009	Glyphosate - Acute Dermal Irritation Study in Rabbits 12173-08 HAG GLP: Y, published: N 2309181 / ASB2012-11423	Y	HAG

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KIIA 5.2.4 (OECD)	Zelenák, V.	2011	Glyphosate technical - Primary skin irritation study in rabbits - Final report Amendment 1 10/218-006N SYN GLP: Y, published: N 2309195 / ASB2012-11427	Y	SYN
KIIA 5.2.5 (OECD)	Arcelin, G.	2007	Glyphosate technical material: Primary eye irritation study in rabbits B02788 (T007038-05) SYN GLP: Y, published: N 2309219 / ASB2012-11437	Y	SYN
KIIA 5.2.5 (OECD)	Brett, M.	1990	Acute eye irritation/corrosion of glyphosate technical in the rabbit AGC-900822 ! AGC-002 ! R234 TOX9500264	N	---
KIIA 5.2.5 (OECD)	Busch, B.	1987	Primary eye irritation of Mon 8722 in New Zealand white rabbits FDRL 9307A ! FD-86-430 TOX9552342	N	---
KIIA 5.2.5 (OECD)	Canabrava Frossard de Faria, B.C.F.	2008	Acute Eye Irritation/Corrosion Study in Rabbits with Glyphosate Technical RF-3996.312.599.07 HAG GLP: Y, published: N 2309213 / ASB2012-11436	Y	HAG
KIIA 5.2.5 (OECD)	Cuthbert, J. A.; Jackson, D.	1989	Glyphosate technical: Primary eye irritation test in rabbits 5886 ! IRI 243268 TOX9552338	N	---
KIIA 5.2.5 (OECD)	Dreher, D. M.	1994	Glyphosate premix: Acute eye irritation test in the rabbit 566-003 ! 545/41 TOX9552340	N	---
KIIA 5.2.5 (OECD)	Hideo, U.	1995	HR-001: Primary Eye Irritation study in rabbits IET 95-0034 ALS GLP: Y, published: N 2309201 / ASB2012-11430	Y	ALS
KIIA 5.2.5 (OECD)	Johnson, I.R.	1997	Glyphosate Acid: Eye Irritation to the Rabbit CTL/P/5138 SYN GLP: Y, published: N 2309217 / TOX2000-1986	Y	SYN
KIIA 5.2.5 (OECD)	Kuhn, J. O.; Harrison, L. V.	1996	CHA 440: Primary eye irritation study in rabbits 2981-96 ! S9-FF81-4.C41 TOX1999-881	N	---

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KIIA 5.2.5 (OECD)	Leuschner, J.	2009	Acute Eye Irritation/Corrosion Test Of Glyphosate TC In Rabbits 24878 HEL GLP: Y, published: N 2309199 / ASB2012-11429	Y	HAG
KIIA 5.2.5 (OECD)	Leuschner, J.	2009	Acute Eye Irritation/Corrosion Test of Glyphosate TC in Rabbits LPT 23914 HAG GLP: Y, published: N 2309205 / ASB2012-11432	Y	HAG
KIIA 5.2.5 (OECD)	Leuschner, J.	2010	Acute Eye Irritation/Corrosion Test of Glyphosate TC in Rabbits LPT 24606 HAG GLP: Y, published: N 2309207 / ASB2012-11433	Y	HAG
KIIA 5.2.5 (OECD)	Merkel, D.	2005	Eye Irritation/Corrosion Effects in Rabbits (*Oryctolagus cuniculus*) of Glyphosate 95 TC PSL 15277 HAG GLP: Y, published: N 2309211 / ASB2012-11435	Y	HAG
KIIA 5.2.5 (OECD)	Reagan, E.L., Laveglia, J.	1988	Primary Eye Irritation Study of Glyphosate FD-88-29 MON GLP: N, published: N 2309215 / Z35395	N	MON
KIIA 5.2.5 (OECD)	Simon, C.	2009	Expert Statement Expert Statement Expert Statement Glyphosate technical: Primary eye irritation study in rat C22897 EXC GLP: Y, published: N 2309203 / ASB2012-11431	Y	EXC
KIIA 5.2.5 (OECD)	Snell, K.	1994	Glyphosate: Acute eye irritation test in the rabbit 710/18 TOX9500249	N	---
KIIA 5.2.5 (OECD)	Suresh, T. P.	1991	Primary eye irritation study with glyphosate technical (FSG 03090 H/05 march 90) in New Zealand white rabbits ES.879.EYE ! TOXI-879/1990 ! ES-GPT-EYE TOX9551093	N	---
KIIA 5.2.5 (OECD)	Talvioja, K.	2007	Glyphosate Technical (NUP 05068): Primary Eye Irritation Study In Rabbits B02305 NUF GLP: Y, published: N 2309197 / ASB2012-11428	Y	NUF

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KIIA 5.2.5 (OECD)	Tavaszi, J.	2011	Glyphosate Technical - Acute Eye Irritation Study in Rabbits 10/218-005N NUF GLP: Y, published: N 2309221 / ASB2012-11438	Y	SYN
KIIA 5.2.5 (OECD)	Tornai, A.; Rozsnyoi, F.; Turczer, K. Arszenovits, S. Dufner,A.	1994	Glyphosate (Alkaloida, Tiszavasvari): Primary eye irritation study in rabbits GHA-93-405/N TOX9650146	N	---
KIIA 5.2.5 (OECD)	Tos, E. G.; Maraschin, R.	1991	Acute eye irritation study in New Zealand White rabbits treated with the test article glyphosate tecnico 98 % 910260 ! PRO496 Z101610	N	---
KIIA 5.2.5 (OECD)	Ullmann, L.; Porricello, T.; Janiak, Th.	1989	Primary eye irritation with glyphosate technical (isopropylamine salt 62 % in water equivalent to 46 % of N-phosphonomethylglycine acid) in the rabbit (rinsed / unrinsed eyes) 238083 ! PRO423 TOX9551629	N	---
KIIA 5.2.5 (OECD)	You, J.	2009	Glyphosate - Acute Eye Irritation Study in Rabbits 12172-08 HAG GLP: Y, published: N 2309209 / ASB2012-11434	Y	HAG
KIIA 5.2.6 (OECD)	Auletta, C. S.	1983	A dermal sensitization study in guinea pigs with Glyphosate BD-83-008 ! B/d 4235-82 Z35238	N	---
KIIA 5.2.6 (OECD)	Betts, C.J.	2007	Glyphosate Technical Material - Skin Sensitisation (Local Lymph Node Assay in the Mouse) GM8048-REG SYN GLP: Y, published: N 2309245 / ASB2012-11449	Y	SYN
KIIA 5.2.6 (OECD)	Cuthbert, J. A.; Jackson, D.	1989	Glyphosate technical: Magnusson-Kligman maximisation test in guinea pigs 5887 ! IRI 243268 TOX9552343	N	---
KIIA 5.2.6 (OECD)	Doyle, C.E.	1996	Glyphosate Acid: Skin Sensitisation to the Guinea Pig CTL/P/4699 SYN GLP: Y, published: N 2309243 / TOX2000-1987	Y	SYN

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KIIA 5.2.6 (OECD)	Dreher, D. M.	1994	Glyphosate premix: Magnusson & Kligman maximisation study in the guinea pig 567-003 ! 545/42 TOX9552345	N	---
KIIA 5.2.6 (OECD)	Haferkorn, J.	2009	Examination of Glyphosate TC in Skin Sensitisation Test in Guinea Pigs according to Magnusson and Kligman (Maximisation Test) LPT 23915 HAG GLP: Y, published: N 2309231 / ASB2012-11443	Y	HAG
KIIA 5.2.6 (OECD)	Haferkorn, J.	2010	Examination Of Glyphosate TC In The Skin Sensitisation Test In Guinea Pigs According To Magnusson And Kligman (Maximisation Test) 24879 HEL GLP: Y, published: N 2309225 / ASB2012-11440	Y	HAG
KIIA 5.2.6 (OECD)	Haferkorn, J.	2010	Examination of Glyphosate TC in Skin Sensitisation Test in Guinea Pigs according to Magnusson and Kligman (Maximisation Test) LPT 24607 HAG GLP: Y, published: N 2309233 / ASB2012-11444	Y	HAG
KIIA 5.2.6 (OECD)	Hideo, U.	1995	HR-001: Dermal sensitisation study in guinea pigs IET 95-0036 ALS GLP: Y, published: N 2309227 / ASB2012-11441	Y	ALS
KIIA 5.2.6 (OECD)	Lima Dallago, B.S.	2008	Skin Sensitisation Test for Glyphosate Technical in Guinea Pigs. Buehler Test RF-3996.318.431.07 HAG GLP: Y, published: N 2309239 / ASB2012-11447	Y	HAG
KIIA 5.2.6 (OECD)	Merkel, D.	2005	Glyphosate acid technical - Dermal Sensitisation in Guinea Pigs (Buehler Method) PSL 15279 HAG GLP: Y, published: N 2309237 / ASB2012-11446	Y	HAG
KIIA 5.2.6 (OECD)	Pore, M. P.; Bhide, M. B.; Naik, P. Y.	1993	Skin sensitisation test in guinea-pigs with glyphosate technical 95 % min of Excel Industries Ltd., Bombay. IIT 1230 TOX9650652	N	---

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KIIA 5.2.6 (OECD)	Richeux, F.	2006	Glyphosate Technical: Skin Sensitisation in the Guinea Pig - Magnusson and Kligman Maximisation method 2060/009 (SMK-PH-05- NUF GLP: Y, published: N 2309241 / ASB2012-11448	Y	NUF
KIIA 5.2.6 (OECD)	Simon, C.	2009	Glyphosate Technical: Contact Hypersensitivity in albino guinea pigs - Maximisation-Test C22908 EXC GLP: Y, published: N 2309229 / ASB2012-11442	Y	EXC
KIIA 5.2.6 (OECD)	Snell, K.	1994	Glyphosate: Magnusson & Kligman maximisation study in the guinea pig 710/19 TOX9500250	N	---
KIIA 5.2.6 (OECD)	Talvioja, K.	2007	Glyphosate Technical (NUP 05068): Contact Hypersensitivity in Albino Guinea Pigs, Maximisation Test B02316 NUF GLP: Y, published: N 2309223 / ASB2012-11439	Y	NUF
KIIA 5.2.6 (OECD)	Török-Bathó, M.	2011	Glyphosate technical - Local lymph node assay in the mouse - Final report amendment 2 10/218-037E SYN GLP: Y, published: N 2309247 / ASB2012-11450	Y	SYN
KIIA 5.2.6 (OECD)	Walker, D. J.; Pateman, J. R.; Jones, J. R.	1991	Luxan glyphosate techn.: Magnusson & Kligman maximisation study in the guinea pig 349/11 TOX9551796	N	---
KIIA 5.2.6 (OECD)	You, J.	2009	Glyphosate - Skin Sensitisation Study in Guinea Pigs. Buehler Test 12174-08 HAG GLP: Y, published: N 2309235 / ASB2012-11445	Y	HAG
KIIA 5.3.1 (OECD)	Atkinson, C.; Perry, C. J.; Hudson, P.; Snodgrass, E.	1989	Glyphosate: 4 week dietary toxicity study in rats 5626 ! IRI 437462 TOX9552351	N	---
KIIA 5.3.1 (OECD)	Goburdhun, R.; Oshodi, R. O.	1989	Glyphosate: Oral maximum tolerated dose study in dogs 5660 ! IRI 640683 TOX9552352	N	---

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KIIA 5.3.1 KIIIA1 7.6.2 (OECD)	Hadfield, N.	2012	Glyphosate acid - *In Vitro* absorption through abraded rabbit skin using [^{14}C]-glyphosate JV2182-REG GTF GLP: Y, published: N 2309282 / ASB2012-11459	Y	EGT
KIIA 5.3.1 (OECD)	Heath, J.; Strutt, A.; Hudson, P.; Iswariah, V.	1993	Glyphosate: 3 week toxicity study in rats with dermal administration 7839 ! IRI 450881 TOX9552367	N	---
KIIA 5.3.1 KIIA 5.3.7 KIIIA1 7.6.2 (OECD)	Johnson, D.E.	1982	21-Day dermal toxicity study in rabbits IR-81-195 MON GLP: N, published: N 2309280 / TOX9552366	N	MON
KIIA 5.3.1 (OECD)	Naylor, M. W.	1982	Range finding study of MON 0139 and iso-propylamine administered orally to dogs ML-81-032/810036 ! MSL-2155 TOX9552349	N	---
KIIA 5.3.1 (OECD)	Pinto, P.J.	1996	Glyphosate acid: 21-day dermal toxicity study in rats CTL/P/4985 SYN GLP: Y, published: N 2309288 / ASB2012-11461	Y	SYN
KIIA 5.3.1 (OECD)	Suresh, T. P.	1991	28-day dietary study in rats on glyphosate technical ES.881.28 DDR ! TOXI-881/1991 ! ES-GPT-28 DDR TOX9551095	N	---
KIIA 5.3.1 (OECD)	Suresh, T. P.	1994	28-day dietary study in rats on glyphosate technical –Amendment ES.881.28 DDR ! TOXI-881/1991 ! ES-GPT-28 DDR Z102035	N	---
KIIA 5.3.1 (OECD)	Suresh, T. P.	1994	28-day dietary study in rats on glyphosate technical - Second Amendment ES.881.28 DDR ! TOXI-881/1991 ! ES-GPT-28 DDR Z102043	N	---
KIIA 5.3.1 KIIA 5.3.7 (OECD)	Tornai, A.	1994	GGlyphosate technical (Alkaloida, Tiszavasvári): Repeated dose twenty-eight-Day dermal toxicity study in rabbits MÜF 214/94 MON GLP: Y, published: N 2309284 / TOX9650151	N	MON

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KIIA 5.3.1 KIIIA1 7.1.3 (OECD)	Velasquez, D. J.	1983	Four-week study of 33-1/3 % use-dilution of Roundup in water administered to male and female Sprague-Dawley rats by inhalation 830025 ! ML-83-015 TOX2002-694	N	---
KIIA 5.3.2 (OECD)	Antal, A.	1981	Glyphosate: Subchronic toxicological study 90-day rats TOX9650152	N	---
KIIA 5.3.2 (OECD)	Botham, P.A.	1996	First Revision to Glyphosate Acid: 90 Day Oral Feeding Study in Rats CTL/P/1599 SYN GLP: Y, published: N 2309249 / TOX2000-1990	Y	SYN
KIIA 5.3.2 (OECD)	Brett, M.;	1990	Glyphosate technical: 90 day oral toxicity study in the rat AGC-900914 ! AGC-401 ! R230 TOX9500266	N	---
KIIA 5.3.2 (OECD)	Coles, L.J., Thomas, O.N., Bartlett, A.J., Brooks, P.N	1996	Technical Glyphosate: Ninety Day Sub-Chronic Oral (Dietary) Toxicity Study In The Rat 434/016 NUF GLP: Y, published: N 2309256 / ASB2012-11451	Y	NUF
KIIA 5.3.2 (OECD)	Eadie, A.;	1989	Glyphosate technical: 90 day oral toxicity study in the rats - incl. Amendment to Protocol BY-401 BY-891002 ! BY-401 TOX9551821	N	---
KIIA 5.3.2 (OECD)	Kinoshita, M.	1995	HR-001: 13-week Subchronic Oral Toxicity Study in Rats IET 94-0138 ALS GLP: Y, published: N 2309258 / ASB2012-11452	Y	ALS
KIIA 5.3.2 (OECD)	Kuwahara	1995	HR-001: 13-week Oral Subchronic Toxicity Study in Mice IET 94-0136 ALS GLP: Y, published: N 2309260 / ASB2012-11453	N	ALS
KIIA 5.3.2 (OECD)	Parker, R.M.	1993	90 day range finding study of glyphosate in rats 011-0001 ALK GLP: Y, published: N 2309252 / TOX9650149	N	ALK

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KIIA 5.3.2 (OECD)	Perry, C. J.; Atkinson, C.; Strutt, A.; Henderson, W.; Hudson, P.	1991	Glyphosate: 13-week dietary toxicity study in rats 7136 ! IRI 437876 TOX9552364	N	---
KIIA 5.3.2 (OECD)	Perry, C. J.; Atkinson, C.; Strutt, A.; Hudson, P.; Jones, M.	1991	Glyphosate: 13-week dietary toxicity study in mice 7024 ! IRI 437918 TOX9552363	N	---
KIIA 5.3.2 (OECD)	Stout, L. D.; Johnson, C. W.	1987	90-day study of glyphosate administered in feed to Sprague-Dawley rats MSL 7375 ! ML-86-351 ! EHL 86128 TOX9552362	N	---
KIIA 5.3.2 (OECD)	Suresh, T. P.	1992	Glyphosat techn. (FSG 03090 H/05 March 1990): 90 day oral toxicity study in wistar rats TOXI-882/1991 ! ES-GPT-90 OR ! ES-882 90 OR TOX9551096	N	---
KIIA 5.3.3 (OECD)	Gaou, I.	2007	Glyphosate Technical: 13-Week Toxicity Study By Oral Route (Capsule) In Beagle Dogs 29646 TCC NUF GLP: Y, published: N 2309262 / ASB2012-11454	Y	NUF
KIIA 5.3.3 (OECD)	Hodge, M.C.E.	1996	First Revision to Glyphosate Acid: 90-Day Oral Toxicity Study in Dogs CTL/P/1802 SYN GLP: Y, published: N 2309271 / TOX2000-1991	Y	SYN
KIIA 5.3.3 (OECD)	Prakash, P.J.	1999	Subchronic (90 Day) Oral Toxicity Study With Glyphosate Technical In Beagle Dogs AND Test compound stability in experimental diet (dog feed) 1816 / 1817-R.FST FSG GLP: Y, published: N 2309264 / ASB2012-11455	Y	ADM
KIIA 5.3.3 (OECD)	Reyna, M.S.	1985	Twelve month study of glyphosate adminis-tered by gelatin capsule to beagle dogs MSL-5069 ! 636 Z35385	N	---
KIIA 5.3.3 (OECD)	Reyna, M. S.; Thake, D.	1983	Six month study of MON 0139 administered by gelatin capsule to beagle dogs 810166 ! ML-81-368 TOX9552361	N	---

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KIIA 5.3.3 (OECD)	Yoshida, A.	1996	HR-001: 13-week Oral Subchronic Toxicity Study in Dogs IET 94-0158 ALS GLP: Y, published: N 2309269 / ASB2012-11456	Y	ALS
KIIA 5.3.4 (OECD)	Brammer, A.	1996	Glyphosate Acid: 1 Year Dietary Toxicity Study in Dogs CTL/P/5079 SYN GLP: Y, published: N 2309278 / TOX2000-1992	Y	SYN
KIIA 5.3.4 (OECD)	Goburdhun, R.	1990	Glyphosate: 52-week oral toxicity study in dogs 7502 ! IRI 642675 TOX9552384	N	---
KIIA 5.3.4 (OECD)	Haag, V.	2007	Glyphosate technical: 52-week Toxicity Study by Oral Route (Capsule)in Beagle Dogs 29647 TCC NUF GLP: Y, published: N 2309274 / ASB2012-11457	Y	NUF
KIIA 5.3.4 (OECD)	Nakashima, N.	1997	HR-001: 12-Month Oral Chronic Toxicity Study in Dogs IET 94-0157 ALS GLP: Y, published: N 2309276 / ASB2012-11458	Y	ALS
KIIA 5.4.1 (OECD)	Akanuma, M.	1995	HR-001: Reverse Mutation Test IET 94-0142 ALS GLP: Y, published: N 2309291 / ASB2012-11462	Y	ALS
KIIA 5.4.1 (OECD)	Callander, R.D.	1996	Glyphosate acid: An evaluation of mutagenic potential using *S. typhimurium* and *E. coli* CTL/P/4874 SYN GLP: Y, published: N 2309313 / ASB2012-11473	Y	SYN
KIIA 5.4.1 (OECD)	Flügge, C.	2009	Mutagenicity Study of Glyphosate TC in the *Salmonella typhimurium* Reverse Mutation Assay (*in vitro*) LPT 23916 HAG GLP: Y, published: N 2309303 / ASB2012-11468	Y	HAG
KIIA 5.4.1 (OECD)	Flügge, C.	2010	Mutagenicity Study of Glyphosate TC in the *Salmonella typhimurium* Reverse Mutation Assay (*in vitro*) LPT 24880 HAG GLP: Y, published: N 2309305 / ASB2012-11469	Y	HAG

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KIIA 5.4.1 (OECD)	Jensen, J. C.	1991	Mutagenicity test: Ames salmonella assay with glyphosate, batch 206-JaK-25-1 Report: 12323, TOX9552371	Y	---
KIIA 5.4.1 KIIIA1 7.6.3 (OECD)	Kier, L. D.; Stegeman, S. D.; Costello, J. G.; Schermes, S.	1992	Ames/salmonella mutagenicity assay of MON 2139 (Roundup herbicide formulation) EHL 91183 ! ML-91-440 ! MSL-11729 TOX1999-239	N	---
KIIA 5.4.1 (OECD)	Kier, L. D.; Stegeman, S. D.; Costello, J. G.; Schermes, S.	1992	Ames/salmonella mutagenicity assay of MON 14445 (DIRECT Herbicide formulation) MSL-11731 ! EHL 91185/ML-91-442 TOX1999-320	N	---
KIIA 5.4.1 KIIA 5.4.4 (OECD)	Kier, L. D.; Stegeman, S. D.; Costello, J. G.; Schermes, S.	1992	Ames/Salmonella mutagenicity assay of Rodeo MSL-11730 ! EHL 91184/ML-91-441 TOX9552373	N	---
KIIA 5.4.1 (OECD)	Li, A. P.; Long, T. J.	1988	An evaluation of the genotoxic potential of glyphosate, Fundamental and Applied Toxi-cology 10 (1988)537 – 546 published: Y, TOX9500253	N	---
KIIA 5.4.1 KIIA 5.4.4 (OECD)	Rank, J.; Jensen, A. G.; Skov, B.	1993	Genotoxicity testing of the herbicide roundup and its active ingredient glyphosate isopropyl-amine using the mouse bone marrow micronu-cleus test, Salmonella mutagenicity test, and Allium anaphase-telephase test Z82234	Y	---
KIIA 5.4.1 KIIA 5.4.4 (OECD)	Rasmussen, E. S.	1997	Genotoxicity of Roundup/Glyphosate, Danish Environmental Protection Agency, AA036753, 7042-0110 ASB2013-9671	N	---
KIIA 5.4.1 (OECD)	Riberri do Val, R.	2007	Bacterial reverse mutation test (Ames Test) for Glifosato Técnico Helm 3393/2007-2.0AM-B HAG GLP: Y, published: N 2309299 / ASB2012-11466	Y	HAG
KIIA 5.4.1 (OECD)	Schreib, G.	2012	Reverse mutation assay using Bacteria (Sal-monella typhimurium) with Glyphosate tech. 126159 ASB2014-9133		

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KIIA 5.4.1 (OECD)	Shirasu, Y.; Moriya, M.; Ota, T.; Ohta, T.	1978	Glyphosate: The report of mutagenic study with bacteria for CP 67573 - Microbial mutagenicity testing on CP67573 Report: ET-78-241, TOX9552368	N	---
KIIA 5.4.1 (OECD)	Sokolowski, A.	2007	*Salmonella typhimurium* and *Escherichia coli* Reverse mutation assay with glyphosate technical (NUP-05068) 1061401 NUF GLP: Y, published: N 2309293 / ASB2012-11463	Y	NUF
KIIA 5.4.1 (OECD)	Sokolowski, A.	2007	*Salmonella typhimurium* and *Escherichia coli* Reverse mutation assay with glyphosate technical (NUP-05070) 1061402 NUF GLP: Y, published: N 2309295 / ASB2012-11464	Y	NUF
KIIA 5.4.1 (OECD)	Sokolowski, A.	2007	*Salmonella typhimurium* and *Escherichia coli* Reverse mutation assay with glyphosate technical (NUP-05067) 1061403 NUF GLP: Y, published: N 2309297 / ASB2012-11465	Y	NUF
KIIA 5.4.1 (OECD)	Sokolowski, A.	2009	Glyphosate technical - *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay 1264500 SYN GLP: Y, published: N 2309315 / ASB2012-11474	Y	SYN
KIIA 5.4.1 (OECD)	Sokolowski, A.	2010	*Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay with Solution of Glyphosate TC spiked with Glyphosine 1332300 HAG GLP: Y, published: N 2309307 / ASB2012-11470	Y	HAG
KIIA 5.4.1 (OECD)	Thompson, P.W.	1996	Technical glyphosate: Reverse mutation assay "Ames test" using *Salmonella typhimurium* and *Escherichia coli* 434/014 NUF GLP: Y, published: N 2309311 / ASB2012-11472	Y	NUF
KIIA 5.4.1 (OECD)	Thompson, P.	2014	Glyphosate: Reverse mutation assay 'Ames test' using Salmonella typhimurium and Escherichia coli 41401854 ASB2014-9148	Y	

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KIIA 5.4.1 (OECD)	Vargas, A. A. T.; Bonetti, R.	1996	The *Salmonella typhimurium* reverse mutation by Glifos G.1.1 - 050/96 TOX1999-884	N	---
KIIA 5.4.1 (OECD)	Wallner, B.	2010	Reverse Mutation Assay using Bacteria (*Salmonella typhimurium*) with Glyphosate TC BSL 101268 HAG GLP: Y, published: N 2309309 / ASB2012-11471	Y	HAG
KIIA 5.4.2 (OECD)	Fox, V.	1998	Glyphosate acid: *In vitro* cytogenetic assay in human lymphocytes CTL/P/6050 SYN GLP: Y, published: N 2309321 / TOX2000-1995	Y	SYN
KIIA 5.4.2 (OECD)	Jensen, J. C.	1991	Mutagenicity test: *In vitro* mammalian cell gene mutation test with glyphosate, batch 206-JaK-25-1, Report: 12325, published: N, TOX9552372	N	---
KIIA 5.4.2 (OECD)	Kyomu, M.	1995	HR-001: *In vitro* cytogenetics test IET 94-0143 ALS GLP: Y, published: N 2309317 / ASB2012-11475	Y	ALS
KIIA 5.4.2 KIIA 5.4.3 KIIA 4.4.4 (OECD)	Li, A. P.	1983	CHO/HGPRT gene mutation assay with glyphosate, Report ML-83-155 ! 830079, published: N, TOX9552369	N	---
KIIA 5.4.2 (OECD)	Rossberger, S.	1994	Glyphosate: DNA repair test with primary rat hepatocytes, Report: 931564 ! 94-03-28 ro, published: N, TOX9400697/ TOX9551099	N	ADM
KIIA 5.4.2 (OECD)	van de Waart, E. J.	1995	Evaluation of the ability of glyphosate to induce chromosome aberrations in cultured peripheral human lymphocytes (with independent repeat) Report: 141918, published: N, TOX9651525	N	---
KIIA 5.4.2 (OECD)	Wright, N.P.	1996	Technical glyphosate: Chromosome aberration test in CHL cells *in vitro* 434/015 NUF GLP: Y, published: N 2309319 / ASB2012-11476	Y	NUF
KIIA 5.4.3 (OECD)	Akanuma, M.	1995	HR-001: DNA Repair Test (Rec-Assay) IET 94-0141 ALS GLP: Y, published: N 2309325 / ASB2012-11477	N	ALS

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KIIA 5.4.3 (OECD)	Clay, P.	1996	Glyphosate acid: L5178 TK+/- mouse lymphoma gene mutation assay CTL/P/4991 SYN GLP: Y, published: N 2309323 / TOX2000-1994	Y	SYN
KIIA 5.4.4 KIIA 5.10 (OECD)	Alvarez-Moya, C., Silva, M.R., Arambula, A.R.V., Sandoval, A.I., Vasquez, H.C., Montes, R.M.G.	2011	Evaluation of genetic damage induced by glyphosate isopropylamine salt using Tradescantia bioassays Genetics and Molecular Biology 34 (1):127-130 34, 127-130 GLP: N, published: Y 2309560 / ASB2012-11538	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Amer, S.M., Aly, F.A.E., Farghaly, A.A., Ibrahim, A.A.E.	2006	*In vitro* and *in vivo* evaluation of the genotoxicity of the herbicide glyphosate in mice Bulletin of the National Research Centre (Egypt) 31, 427-446 GLP: N, published: Y 2309562 / ASB2012-11539	N	MOD
KIIA 5.4.4 KIIA 5.10 (OECD)	Andre, V., Goff, J.L., Pottier, D., Lebailly, P., Peluso, M., Munnia, A., Gauduchon, P.	2007	Evaluation of bulky DNA adduct levels after pesticide use: Comparison between open-field farmers and fruit growers Toxicological & Environmental Chemistry 89, 125-139 GLP: N, published: Y 2309570 / ASB2012-11543	N	LIT
KIIA 5.4.4 KIIA 5.5.3 KIIA 5.6 KIIA 5..7.2 KIIA 5.10 KIIIA1 7.6.3 (OECD)	Anonym.	2004	WORLD HEALTH ORGANIZATION and FOOD AND AGRICULTURE ORGANIZA-TION OF THE UNITED NATIONS, Rome: Pesticide residues in food – 2004; Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Envi-ronment and the WHO Core Assessment Group on Pesticide Residues Rome, Italy, 20–29 September 2004, ASB2008-6266	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Benachour, N., Seralini, G.E.	2009	Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells Chem Res Toxicol 22, 97-105 GLP: N, published: Y 2309606 / ASB2012-11561	N	LIT

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KIIA 5.4.4 KIIA 5.10 (OECD)	Bolognesi, C., Bonatti, S., Degan, P., Gallerani, E., Peluso, M., Rabboni, R., Roggieri, P., Abbondandolo, A.	1997	Genotoxic activity of glyphosate and its technical formulation roundup Journal of Agricultural and Food Chemistry 45, 1957-1962 GLP: N, published: Y 2309628 / Z59299	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Bolognesi, C., Carrasquilla, G., Volpi, S., Solomon, K.R., Marshall, E.J.	2009	Biomonitoring of genotoxic risk in agricultural workers from five colombian regions: association to occupational exposure to glyphosate J Toxicol Environ Health A 72, 986-997 GLP: N, published: Y 2309630 / ASB2012-11570	N	JCC
KIIA 5.4.4 KIIA 5.10 (OECD)	Bolognesi, C., Landini, E., Perrone, E., Roggieri, P.	2004	Cytogenetic biomonitoring of a floriculturist population in Italy: micronucleus analysis by fluorescence in situ hybridization (FISH) with an all-chromosome centromeric probe Mutation Research-Genetic Toxicology and Environmental Mutagenesis 557, 109-117 GLP: N, published: Y 2309634 / ASB2012-11572	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Bolognesi, C., Perrone, E., Landini, E.	2002	Micronucleus monitoring of a floriculturist population from western Liguria, Italy Mutagenesis 175, 391-397 GLP: N, published: Y 2309636 / ASB2012-11573	N	LIT
KIIA 5.4.4 (OECD)	Carvalho Marques, M.F.	1999	A micronucleus study in mice for glifosate técnico Nufarm RF-G12.79/99 NUF GLP: Y, published: N 2309335 / ASB2012-11482	Y	NUF
KIIA 5.4.4 KIIA 5.10 KIIIA1 7.6.3 (OECD)	Cavalcante, D.G.S.M., Martinez, C.B.R., Sofia, S.H.	2008	Genotoxic effects of Roundup (R) on the fish *Prochilodus lineatus* Mutation Research-Genetic Toxicology and Environmental Mutagenesis 655, 41-46 GLP: N, published: Y 2309662 / ASB2012-11586	N	LIT

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KIIA 5.4.4 KIIA 5.10 (OECD)	Cavas, T., Konen, S.	2007	Detection of cytogenetic and DNA damage in peripheral erythrocytes of goldfish (*Carassius auratus*) exposed to a glyphosate formulation using the micronucleus test and the comet assay Mutagenesis 22, 263-268 GLP: N, published: Y 2309664 / ASB2012-11587	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Chruscielska, K.; Brzezinski, J.; Grafstein, B.	2000	Glyphosate: Evaluation of chronic activity and possible far -reaching effects - Part 2. Studies on mutagenic activity Pestycydy, 2000, (3-4), 21-25 ASB2013-9830	N	---
KIIA 5.4.4 KIIA 5.10 KIIIA1 7.6.3 (OECD)	Clements, C.; Ralph, S.; Pe-tras, M.	1997	Glyphosate: Genotoxicity of select herbicides in *Rana catesbeiana* tadpoles using the alka-line single-cell gel DNA electrophoresis (com-et) assay Environ. Molec. Mutagen., 29, 277-288 Z101728	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Coutinho do Nascimento; A. C.; Grisolia, C. K.;	2000	Comparative analysis between micronuclei tests in mice and in peripheral erythrocytes of *Oreochromis niloticus* in evaluation ofmutagenic potential ofthe agrotoxins deltamethrin, dicofol, glyphosate, and lmazapyr ASB2013-11477	N	---
KIIA 5.4.4 (OECD)	Costa, K. C.	2010	Amendment No. 1 to report: Evaluation of the mutagenic potential of Glyphosate technical by micronucleus assay in mice 3996.402.395.07 ASB2014-9284		
KIIA 5.4.4 (OECD)	Costa, K. C.	2008	Evaluation of the mutagenic potential of Glyphosate Technical Micronucleus assay in mice Bioagri Laboratories Ltda., Brazil Data owner: HAG (original sponsor: Jingma Chemicals, Longyou Zhejian, China) Report No.: RF - 3996.402.395.07 Date: 2008-09-29 Unpublished; ASB2012-11481		
KIIA 5.4.4 KIIA 5.5.3 KIIA 5.10 (OECD)	Chruscielska, K.; Brzezinski, J.; Kita, K.	2000	Glyphosate: Evaluation of chronic activity and possible far - reaching effects - Part 1. Studies on chronic toxicity Pestycydy, 2000, (3 -4), 11-20 ASB2013-9829	N	---

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KIIA 5.4.4 KIIA 5.10 (OECD)	Chruscielska, K.; Brzezinski, J.; Kahlhorn, D.	2000	Glyphosate: Evaluation of chronic activity and possible far - reaching effects - Part 3. Prenatal toxicity Pestycydy, 2000, (3-4), 27-31 ASB2013-9831	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Dimitrov, B.D., Gadeva, P.G., Benova, D.K., Bineva, M.V.	2006	Comparative genotoxicity of the herbicides Roundup, Stomp and Reglone in plant and mammalian test systems Mutagenesis 21, 375-382 GLP: N, published: Y 2309708 / ASB2012-11607	N	LIT
KIIA 5.4.4 (OECD)	Durward, R.	2006	Glyphosate Technical: Micronucleus Test In The Mouse 2060/014 NUF GLP: Y, published: N 2309327 / ASB2012-11478	Y	NUF
KIIA 5.4.4 (OECD)	Flowers, L. J.	1981	Ames/salmonella mutagenicity assay of MON 8080 MSL 1538 ! ML-80-294/800281 TOX1999-319	N	---
KIIA 5.4.4 (OECD)	Flügge, C.	2009	Micronucleus Test of Glyphosate TC in Bone Marrow Cells of the CD Rat by oral administration LPT 23917 HAG GLP: Y, published: N 2309329 / ASB2012-11479	Y	HAG
KIIA 5.4.4 (OECD)	Fox, V., Mackay, J.M.	1996	Glyphosate acid: mouse bone marrow micronucleus test CTL/P/4954 SYN GLP: Y, published: N 2309337 / TOX2000-1996	N	SYN
KIIA 5.4.4 KIIA 5.10 (OECD)	Grisolia, C.K.	2002	A comparison between mouse and fish micronucleus test using cyclophosphamide, mitomycin C and various pesticides Mutation Research-Genetic Toxicology and Environmental Mutagenesis 518, 145-150 GLP: N, published: Y 2309776 / ASB2012-11834	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Guilherme, S., Gaivão, I., Santos, M.A., Pacheco, M.	2010	European eel (*Anguilla anguilla*) genotoxic and pro-oxidant responses following short-term exposure to Roundup®a glyphosate-based herbicide Mutagenesis 25, 523-530 GLP: N, published: Y 2309780 / ASB2012-11836	N	LIT

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KIIA 5.4.4 KIIA 5.10 (OECD)	Helal, A.D., Moussa, H.M.	2005	Chromosomal aberrations induced by glyphosate isopropylamine herbicide and trials for diminuting its toxicity using some chemical inactivators and antioxidant Veterinary Medical Journal Giza 53, 169-187 GLP: N, published: Y 2309794 / ASB2012-11841	N	LIT
KIIA 5.4.4 KIIA 5.10 KIIIA1 7.6.3 (OECD)	Heydens, W.F., Healy, C.E., Hotz, K.J., Kier, L.D., Martens, M.A., Wilson, A.G.E, Farmer, D.R.	2008	Genotoxic potential of glyphosate formulations: Mode-of-action investigations Journal of Agricultural and Food Chemistry 56, 1517-1523 GLP: N, published: Y 2309802 / ASB2012-11845	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Holeckova, B.	2006	Evaluation of the *in vitro* effect of glyphosate-based herbicide on bovine lymphocytes using chromosome painting Bulletin of the Veterinary Research Institute in Pulawy 50, 533-536 GLP: N, published: Y 2309806 / ASB2012-11847	N	LIT
KIIA 5.4.4 (OECD)	Honarvar, N.	2008	Glyphosate Technical - Micronucleus Assay in Bone Marrow Cells of the Mouse 1158500 SYN GLP: Y, published: N 2309339 / ASB2012-11483	Y	SYN
KIIA 5.4.4 (OECD)	Jensen, J. C.	1991	Mutagenicity test: Micronucleus test with glyphosate, batch 206-JaK-25-1, Report: 12324, published: N, TOX9552374	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Kale, P.G., Petty, B.T., Walker, S., Ford, J.B., Dehkordi, N., Tarasia, S., Tasie, B.O., Kale, R., Sohni, Y.R.	1995	Mutagenicity testing of 9 herbicides and pesticides currently used in agriculture Environmental and Molecular Mutagenesis 25, 148-153 GLP: N, published: Y 2309834 / Z73986, ASB2012-11860	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Kaya, B.: Creus, A.; Yanikoglu, A.; et al.;	2000	Use of the Drosophila wing spot test in the genotoxicity testing of different herbicides ASB2013-9832	N	---
KIIA 5.4.4 (OECD)	Kier, L. D.; Flowers, L. J.; Huffman, M. B.	1992	Mouse micronucleus study of Rodeo herbicide formulation MSL-11772 ! EHL 91201/91205/ML-91-438 TOX9552376	N	---

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KIIA 5.4.4 KIIIA1 7.6.3 (OECD)	Kier, L. D.; Flowers, L. J.; Huffman, M. B.	1992	Mouse micronucleus study of Roundup herbicide formulation MSL-11771 ! EHL 91200/91204 ! ML-91-434/ML-91-437 TOX1999-242	N	---
KIIA 5.4 .4 (OECD)	Kier, L. D.; Flowers, L. J.; Huffman, M. B.	1992	Glyphosate: Mouse micronucleus study of DIRECT Herbicide formulation MSL-11773 ! EHL 91202/91206 ! ML-91-436/ML-91-439 TOX1999-322	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Knopper, L.D., Lean, D.R.S.	2004	Carcinogenic and genotoxic potential of turf pesticides commonly used on golf courses Journal of Toxicology and Environmental Health-Part B-Critical Reviews 7, 267-279 GLP: N, published: Y 2309864 / ASB2012-11871	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Lebailly, P., Devaux, A., Pottier, D., De Meo, M., Andre, V., Baldi, I., Severin, F., Bernaud, J., Durand, B., Henry-Amar, M., Gauduchon, P.	2003	Urine mutagenicity and lymphocyte DNA damage in fruit growers occupationally exposed to the fungicide captan Occupational & Environmental Medicine 60, 910-917 GLP: N, published: Y 2309878 / ASB2012-11878	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Levine, S.L., Han, Z., Liu, J., Farmer, D.R., Papadopoulos, V.	2007	Disrupting mitochondrial function with surfactants inhibits MA-10 Leydig cell steroidogenesis Cell Biol Toxicol 23, 385-400 GLP: N, published: Y 2309890 / ASB2009-9030	N	LIT
KIIA 5.4.4 (OECD)	Li, A. P.	1983	*In vivo* bone marrow cytogenetics study of glyphosate in Sprague-Dawley rats, Report: ML-83-236 ! 830083, published: N, TOX9552375	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Lioi, M. B.; Scarfi, M. R.; Santoro, A.	1998	Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures *in vitro* Mutation Research 403 (1998) 13-20 ASB2013-9836	N	---

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KIIA 5.4.4 KIIA 5.10 (OECD)	Lioi, M. B.; Scarfi, M. R.; Santoro, A.	1998	Cytogenetic damage and induction of pro-oxidant state in human lymphocytes exposed *in vitro* to glyphosate, vinclozolin,aAtrazine and DPX-E9636 Environmental and Molecular Mutagenesis 32: 39-46 (1998) ASB2013-9837	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Manas, F., Peralta, L., Raviolo, J., Ovandoa, H.G., Weyers, A., Ugnia, L., Cid, M.G., Larripa, I., Gorla, N.	2009	Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests Environmental Toxicology and Pharmacology 28, 37-41 GLP: N, published: Y 2309908 / ASB2012-11892	N	LIT
KIIA 5.4.4 KIIA 5.10 KIIIA1 7.6.3 (OECD	Martinez, T. T.; Brown, K.	1991	Glyphosate: Oral and pulmonary toxicology of the surfactant used in Roundup herbicide Z80636	N	---
KIIA 5.4.4 KIIA 5.11 (OECD)	Mensink, H.; Janssen, P.; WHO	1994	Environmental health criteria 159, Glyphosate TOX9500301	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Mladinic, M., Berend, S., Vrdoljak, A.L., Kopjar, N., Radic, B., Zeljezic, D.	2009	Evaluation of genome damage and its relation to oxidative stress induced by glyphosate in human lymphocytes in vitro Environmental and Molecular Mutagenesis 50, 800-807 GLP: N, published: Y 2309942 / ASB2012-11906	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Mladinic, M., Perkovic, P., Zeljezic, D.	2009	Characterization of chromatin instabilities induced by glyphosate, terbuthylazine and carbofuran using cytome FISH assay Toxicol Lett 189, 130-137 GLP: N, published: Y 2309944 / ASB2012-11907	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Monroy, C., Cortes, A., Sicard, D., de Restrepo, H.	2005	Cytotoxicity and genotoxicity of human cells exposed *in vitro* to glyphosate Biomedica 25, 335-345 GLP: N, published: Y 2309950 / ASB2012-11910	N	LIT

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KIIA 5.4.4 KIIA 5.10 (OECD)	Pastor, S., Creus, A., Parron, T., Cebulska-Wasilewska, A., Siffel, C., Piperakis, S., Marcos, R.	2003	Biomonitoring of four European populations occupationally exposed to pesticides: use of micronuclei as biomarkers Mutagenesis 18, 249-258 GLP: N, published: Y 2310004 / ASB2012-11991	N	LIT
KIIA 5.4.4 (OECD)	Patel, N. N.	2012	Micronucleus test of Glyphosate TGAI in mice 120709 ! 485-1-06-4696 ! DR-0112-6927-003 ! 10001701-27-1 ASB2014-9277		
KIIA 5.4.4 KIIA 5.10 (OECD)	Paz-Y-Mino, C., Sanchez, M.E., Arevalo, M., Munoz, M.J., Witte, T., De-La-Carrera, G.O., Leone, P.E.	2007	Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate Genetics and Molecular Biology 30, 456-460 GLP: N, published: Y 2310006 / ASB2012-11992	N	LIT
KIIA 5.4.4 KIIA 5.10 KIIIA1 7.6.3 (OECD)	Peluso, M., Munnia, A., Bolognesi, C., Parodi, S.	1998	32P-postlabeling detection of DNA adducts in mice treated with the herbicide Roundup Environmental and Molecular Mutagenesis 31, 55-59 GLP: N, published: Y 2310014 / TOX1999-318	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Piesova, E.	2004	The Influence Of Different Treatment Length On the Induction Of Micronuclei In Bovine Lymphocytes After Exposure To Glyphosate Folia Veterinaria 48, 130-134 GLP: N, published: Y 2310026 / ASB2012-12001	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Piesova, E.	2005	The effect of glyphosate on the frequency of micronuclei in bovine lymphocytes *in vitro* Acta Veterinaria-Beograd 55, 101-109 GLP: N, published: Y 2310024 / ASB2012-12000	N	MOD
KIIA 5.4.4 KIIA 5.10 (OECD)	Poletta, G.L., Larriera, A., Kleinsorge, E., Mudry, M.D.	2009	Genotoxicity of the herbicide formulation Roundup (R) (glyphosate) in broad-snouted caiman (*Caiman latirostris*) evidenced by the Comet assay and the Micronucleus test Mutation Research-Genetic Toxicology and Environmental Mutagenesis 672, 95-102 GLP: N, published: Y 2310028 / ASB2012-12002	N	LIT

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KIIA 5.4.4 KIIA 5.10 (OECD)	Prasad, S., Srivastava, S., Singh, M., Shukla, Y.	2009	Clastogenic effects of glyphosate in bone marrow cells of swiss albino mice J Toxicol GLP: N, published: Y 2310034 / ASB2012-12005	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Raipulis, J., Toma, M., Balode, M.	2009	Toxicity and genotoxicity testing of Roundup Proceedings of the Latvian Academy of Sciences. Section B. Natural, Exact, and Applied Sciences. 63, 29-32 GLP: N, published: Y 2310040 / ASB2012-12008	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Rodrigues, H.G., Penha-Silva, N., Araujo, M.F.P, Nishijo, H., Aversi-Ferreira, T.A.	2011	Effects of Roundup Pesticide on the Stability of Human Erythrocyte Membranes and Micronuclei Frequency in Bone Marrow Cells of Swiss Mice Open Biology Journal 54-59 GLP: N, published: Y 2310046 / ASB2012-12010	N	LIT
KIIA 5.4.4 (OECD)	Roth, M.		Glyphosate technical - Micronucleus assay in bone marrow cells of the mouse 1479200 ! TK0112981 ASB2014-9333		
KIIA 5.4.4 KIIA 5.10 (OECD)	Salvagni, J., Ternus, R., Fuentefria, A.	2011	Assessment of the genotoxic impact of pesticides on farming communities in the countryside of Santa Catarina State, Brazil Genetics and Molecular Biology 34, 122-126 GLP: N, published: Y 2310060 / ASB2012-12017	N	LIT
KIIA 5.4.4 KIIA 5.9 KIIIA1 7.6.3 (OECD)	Sawada, Y., Nagai, Y.	1987	Roundup® poisoning - its clinical observation possible involvement - englische Version Journal of Clinical and Experimental Medicine (paper) 143, 25-27 GLP: N, published: Y 2309502 / Z35531	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Shaham, J., Kaufman, Z., Gurvich, R., Levi, Z.	2001	Frequency of sister-chromatid exchange among greenhouse farmers exposed to pesticides Mutat Res 491-, 71-80 GLP: N, published: Y 2310076 / ASB2012-12025	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Sivikova, K., Dianovsky, J.	2006	Cytogenetic effect of technical glyphosate on cultivated bovine peripheral lymphocytes Int J Hyg Environ Health 209, 15-20 GLP: N, published: Y 2310084 / ASB2012-12029	N	LIT

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KIIA 5.4.4 KIIA 5.8.1 (OECD)	Stammberger, I.;	1992	Dodigen 4022: Chromosome aberrations in vitro in V79 chinese hamster cells 92.1024 ! 92.0337 TOX1999-325	N	---
KIIA 5.4.4 KIIA 5.8.1 (OECD)	Stammberger, I.; Mayer, D.	1992	Dodigen 4022: Study of the mutagenic potential in strains of *Salmonella typhimurium* (ames test) and *Escherichia coli* 92.0487 ! 92.0336 TOX1999-324	N	---
KIIA 5.4.4 KIIA 5.10 KIIIA1 7.6.3 (OECD)	Stegeman, S. D.; Kier, L. D.	1998	Mouse micronucleus screening assay of MON 0818 ML-89-463 ! EHL 89182 TOX1999-240	N	---
KIIA 5.4.4 KIIIA1 7.6.3 (OECD)	Stegeman, S. D.; Li, A. P.	1990	Ames/salmonella mutagenicity assay of MON 0818 EHL 89178 ! ML-89-461 ! MSL-10625 TOX1999-241	N	---
KIIA 5.4.4 (OECD)	Suresh, T.P.	1993	Glyphosate technical (FSG 03090 H/05 March 1990): Mutagenicity-micronucleus test in swiss albino mice, Report: 889-MUT.MN ! TOXI-889/1993 ! ES-GPT-MUT-MN, published: N, TOX9551100	N	---
KIIA 5.4.4 (OECD)	Suresh, T. P.; Ponnanna, D.; Asha, M. et al.	1994	Glyphosate technical (FSG 03090 H/05 March 1990): Genetic toxicology - *In vivo* mammalian bone marrow cytogenetic test, Report: 890-MUT-CH.AB ! TOXI-890/1993 ! ES-GPT-MUT-CH.AB, published: N, TOX9400323 / TOX9551101	N	---
KIIA 5.4.4 KIIA 5.10 (OECD)	Vigfusson, N.V., Vyse, E.R.	1980	The effect of the pesticides Dexon, Captan and Roundup on sister chromatid exchanges in human lymphocytes *in vitro* Mutation Research 79, 53-57 GLP: N, published: Y 2310114 / TOX970056 / ASB2012-12044	N	LIT
KIIA 5.4.4 KIIA 5.10 (OECD)	Vlastos, D., Stivaktakis, P., Matthopoulos, D.P.	2006	Pesticide exposure and genotoxicity correlations within a Greek farmers' group International Journal of Environmental Analytical Chemistry 86, 215-223 GLP: N, published: Y 2310116 / ASB2012-12045	N	LIT
KIIA 5.4.4 KIIA 5.5.3 KIIA 5.10 KIIIA1 7.6.3 (OECD)	Williams, G.M., Kroes, R., Munro, I.C.	2000	Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans Regulatory Toxicology and Pharmacology 31, 117-165 GLP: N, published: Y 2310132 / ASB2012-12053	N	LIT

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KIIA 5.4.4 (OECD)	Zaccaria, C. B.; Vargas, A. A. T.	1996	A micronucleus study in mice for the product GILFOS G1206096 ! G.1.2 - 60/96 TOX1999-253	N	---
KIIA 5.4.4 (OECD)	Zoriki Hosomi, R.	2007	Mammalian Erythrocyte Micronucleus Test for Glifosato Técnico Helm 3393/2007-3.0MN-B ASB2012-11480		
KIIA 5.4.6 (OECD)	Suresh, T. P. et al.	1992	Glyphosate technical (FSG 03090 H/05, March 1990): Dominant lethal test in wistar rats Report: 888-DLT ! TOXI-888/1992 ! ES-GPT-DLT, published: N, TOX9551102	N	---
KIIA 5.4.6 (OECD)	Wrenn, J. M.; Rodwell, D. E.; Jessup, D. C.	1980	Dominant lethal mutagenicity assay with technical Glyphosate in mice, Report: 401-064 ! IR-79-014, published: N, TOX9552377	N	---
KIIA 5.5 (OECD)	Anon.	2015	Lesion-related incidence data. RITA database ASB2015-2532		
KIIA 5.5 (OECD)	Eaton, G.; Johnson, F. N.; Custer, R. P.; Crane, A. R.;	1980	The Icr:Ha(ICR) mouse: a current account of breeding, mutations, diseases and mortality Lab. Animals 14(1980)17-24 ASB2015-2537		LIT
KIIA 5.5 (OECD)	Giknis, M. L. A.; Clifford, C. B.;	2010	Spontaneous neoplastic lesions in the Crl:CD1 (ICR) mouse in control groups from 18 month to 2 year studies Selected pages ASB2015-2529		
KIIA 5.5 (OECD)	Greim, H.; Saltmiras, D.; Mostert, V.; Strupp, C.;	2015	Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies Crit Rev Toxicol, 2015; 45(3): 185–208 ASB2015-2287		LIT
KIIA 5.5 (OECD)	Roe, F. J. C.; Tucker, M. J.;	1974	Recent developments in the design of carcinogenicity tests on laboratory animals Proc. Europ. Soc. Stud. Drug Tox., 15:171-177 (1974) ASB2015-2534		LIT
KIIA 5.5 (OECD)	Sher, S. P.	1974	Review article - Tumors in control mice: Literature tabulation Toxicol. Appl. Pharmacol. 30(1974)337-359 Z22020		LIT
KIIA 5.5 (OECD)	Son, W.-C.; Gopinath, C.;	2004	Early occurrence of spontaneous tumors in CD-1 mice and Sprague–Dawley rats Toxicologic Pathology, 32:371–374, 2004 ASB2015-2533		LIT

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KIIA 5.5 (OECD)	Taddesse-Heath, L.; Chattopadhyay, S. K.; Dillehay, D. L.; et al.;	2000	Lymphomas and high-level expression of murine leukemia viruses in CFW mice J. Virol. 74(2000)15:6832-6837 ASB2015-2535		LIT
KIIA 5.5 (OECD)	Toth, B.; Rappaport, H.; Shubik, P.;	1963	Influence of dose and age on the induction of malignant lymphomas and other tumors by 7,12-Dimethylbenz(α)anthracene in Swiss mice J. Nat. Cancer Institute, 30(1963)4:723-732 ASB2015-2536		LIT
KIIA 5.5 (OECD)	Tucker, M. J.	1979	The effect of long-term food restriction on tumours in rodents Int. J. Cancer: 23, 803-807 (1979) Z83266		LIT
KIIA 5.5 (OECD)	Wood, E.;	2010	Historical Incidence of Malignant lymphoma in CD-1 Mouse ASB2015-2531		
KIIA 5.5.1 KIIA 5.10 (OECD)	Milburn, G.M.	1996	Glyphosate Acid: One Year Dietary Toxicity Study in Rats CTL/P/5143 SYN GLP: Y, published: N 2309341 / TOX2000-1998	N	SYN
KIIA 5.5.2 (OECD)	Atkinson, C., Strutt, A.V., Henderson, W., Fich, J., Hudson, P.	1993	Glyphosate - 104 week combined chronic feeding / oncogenicity study in rats with 52 week interim kill (results after 104 weeks) 7867 CHE GLP: Y, published: N 2309374 / TOX9750499	N	CHE
KIIA 5.5.2 KIIA 5.10 (OECD)	Brammer, A.	2001	Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats CTL/PR1111 SYN GLP: Y, published: N 2309368 / ASB2012-11488	N	SYN
KIIA 5.5.2 (OECD)	Calandra, J. C.	1974	2-year chronic oral toxicity study with CP 67573 in albino rats B564 ! BTL-71-32 Z35230	N	---
KIIA 5.5.2 (OECD)	Enomoto, A.	1997	HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 1 (Seite 1-500) IET 94-0150 Vol.1 ALS GLP: Y, published: N 2309360 / ASB2012-11484	N	ALS

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KIIA 5.5.2 (OECD)	Enomoto, A.	1997	HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 2 (Seite 501-1000) IET 94-0150 Vol. 2 ALS GLP: Y, published: N 2309362 / ASB2012-11485	N	ALS
KIIA 5.5.2 (OECD)	Enomoto, A.	1997	HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol.3 (Seite 1001-1500) IET 94-0150 Vol. 3 ALS GLP: Y, published: N 2309364 / ASB2012-11486	N	ALS
KIIA 5.5.2 (OECD)	Enomoto, A.	1997	HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats, Vol. 4 (Seite 1501-2051) IET 94-0150 Vol. 4 ALS GLP: Y, published: N 2309366 / ASB2012-11487	N	ALS
KIIA 5.5.2 (OECD)	Stout, L.D., Ruecker, F.A.	1990	Chronic study of glyphosate administered in feed to Albino rats MSL-10495 MON GLP: Y, published: N 2309384 / TOX9300244	N	MON
KIIA 5.5.2 (OECD)	Suresh, T.P.	1996	Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats TOXI:886.C.C-R FSG GLP: Y, published: N 2309343 / TOX9651587 / TOX9600015	N	ADM
KIIA 5.5.2 (OECD)	Wood, E., Dunster, J., Watson, P. Brooks, P.	2009	Glyphosate Technical: Dietary combined chronic toxicity / carcinogenicity study in the rat SPL2060-0012 NUF GLP: Y, published: N 2309391 / ASB2012-11490	Y	NUF
KIIA 5.5.3 KIIA 5.10 (OECD)	Acquavella, J.F., Gustin, C., Alexander, B.H., Mandel, J.S.	2005	Implications for epidemiologic research on variation by pesticide in studies of farmers and their families Scandinavian Journal of Work Environment & Health 31, 105-109 GLP: N, published: Y 2309540 / ASB2012-11530	N	LIT

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KIIA 5.5.3 KIIA 5.10 (OECD)	Alavanja, M.C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C.F., Knott, C., Thomas, K., Hoppin, J.A., Barker, J., Coble, J., Sandler, D.P., Blair, A.	2003	Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort Am J Epidemiol 157, 800-814 GLP: N, published: Y 2309554 / ASB2012-11535	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Andreotti, G., Freeman, L.E.B., Hou, L., Coble, J., Rusiecki, J., Hoppin, J.A., Silverman, D.T., Alavanja, M.C.R.	2009	Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort International Journal of Cancer 124, 2495-2500 GLP: N, published: Y 2309572 / ASB2012-11544	N	LIT
KIIA 5.5.3 (OECD)	Atkinson, C.; Martin, T.; Hudson, P.; Robb, D.	1993	Glyphosate: 104-week dietary carcinogenicity study in mice 7793 ! IRI 438618 TOX9552382	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Band, P.R., Abanto, Z., Bert, J., Lang, B., Fang, R., Gallagher, R.P., Le, N.D.	2011	Prostate Cancer Risk and Exposure to Pesticides in British Columbia Farmers Prostate 71, 168-183 GLP: N, published: Y 2309594 / ASB2012-11555	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Barale-Thomas, E.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 473–474 ASB2013-10998	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Berry, C.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 445–446 ASB2013-10988	N	--
KIIA 5.5.3 KIIA 5.10 (OECD)	Blair, A., Freeman, L.B.	2009	Epidemiologic Studies in Agricultural Populations: Observations and Future Directions Journal of Agromedicine 14, 125-131 GLP: N, published: Y 2309618 / ASB2012-11566	N	LIT

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KIIA 5.5.3 KIIA 5.10 (OECD)	Carreon, T., Butler, M.A., Ruder, A.M., Waters, M.A., Davis-King, K.E., Calvert, G.M., Schulte, P.A., Connally, B., Ward, E.M., Sanderson, W.T., Heinemann, E.F., Mandel, J.S., Morten, R.F., Reding, D.J., Rosenmann, K.D., Talaska, G.	2005	Gliomas and farm pesticide exposure in women: The Upper Midwest Health Study Environmental Health Perspectives 113, 546-551 GLP: N, published: Y 2309660 / ASB2012-11585	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	McDuffie, H.H., Pahwa, P., McLaughlin, J.R., Spinelli, J.J., Fincham, S., Dosman, J.A., Robson, D., Skinnider, L.F., Choi, N.W.	2001	Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health Cancer Epidemiol Biomarkers Prev 10, 1155-1163 GLP: N, published: Y 2309924 / ASB2011-364	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Engel, L.S., Hill, D.A., Hoppin, J.A., Lubin, J.H., Lynch, C.F., Pierce, J., Samanic, C., Sandler, D.P., Blair, A., Alavanja, M.C.	2005	Pesticide use and breast cancer risk among farmers' wives in the agricultural health study American Journal of Epidemiology 161, 121-135 GLP: N, published: Y 2309720 / ASB2012-11613	N	MOD
KIIA 5.5.3 KIIA 5.10 (OECD)	Eriksson, M., Hardell, L., Carlberg, M., Akerman, M.	2008	Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis Int J Cancer 123, 1657-1663 GLP: N, published: Y 2309722 / ASB2012-11614	N	LIT

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KIIA 5.5.3 KIIA 5.10 (OECD)	Farmer, D.R., Lash, T.L., Acquavella, J.F.	2005	Glyphosate Results Revisited Environmental Health Perspectives 113, A365-A366 GLP: N, published: Y 2309726 / ASB2012-11616	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Flower, K.B., Hoppin, J.A., Lynch, C.F., Blair, A., Knott, C., Shore, D.L., Sandler, D.P.	2004	Cancer risk and parental pesticide application in children of agricultural health study participants Environmental Health Perspectives 112, 361-635 GLP: N, published: Y 2309734 / ASB2012-11620	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Freeman,L.B.	2009	Evaluation of agricultural exposures: the agricultural health study and the agricultural cohort consortium Reviews on Environmental Health 24, 311-318 GLP: N, published: Y 2309740 / ASB2012-11623	N	MOD
KIIA 5.5.3 KIIA 5.10 (OECD)	Fritschi, L., Benke, G., Hughes, A.M., Kricker, A..,Turner, J., Vajdic, C.M., Grulich, A., Milliken, S., Kaldor, J., Armstrong, B.K.	2005	Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma American Journal of Epidemiology 162, 849-857 GLP: N, published: Y 2309746 / ASB2012-11624	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	George, J., Prasad, S., Mahmood, Z., Shukla, Y.	2010	Studies on glyphosate-induced carcinogenicity in mouse skin: a proteomic approach J Proteomics 73, 951-964 GLP: N, published: Y 2309766 / ASB2012-11829	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Grunewald, W.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 447–448 ASB2013-11001	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Hammond, B.; Goldstein, D. A.; Saltmiras, D.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 459–464 ASB2013-10995	N	---

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KIIA 5.5.3 KIIA 5.10 (OECD)	Hardell, L., Eriksson, M.	1999	A case-control study of non-Hodgkin lymphoma and exposure to pesticides Cancer 85, 1353-1360 GLP: N, published: Y 2309788 / ASB2012-11838	N	MOD
KIIA 5.5.3 KIIA 5.10 (OECD)	Hardell, L., Eriksson, M., Nordstrom, M.	2002	Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: Pooled analysis of two Swedish case-control studies Leukemia & Lymphoma 43, 1043-1049 GLP: N, published: Y 2309790 / ASB2012-11839	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Heinemann, J. A.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 442 ASB2013-10987	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Karunanayake, C.P., Spinelli, J.J., McLaughlin, J.R., Dosman, J.A., Pahwa, P., McDuffie, H.H.	2011	Hodgkin Lymphoma and Pesticides Exposure in Men: A Canadian Case-Control Study Journal of Agromedicine 17, 30-39 GLP: N, published: Y 2309844 / ASB2012-11865	N	LIT
KIIA 5.5.3 (OECD)	Knezevich, A. L.; Hogan, G. K.	1983	A chronic feeding study of glyphosate (Roundup technical) in mice 77-2061 ! (BDN-77-420) TOX9552381	N	---
KIIA 5.5.3 (OECD)	Kumar, D.P.S.	2001	Carcinogenicity Study with Glyphosate Technical in Swiss Albino Mice TOXI: 1559.CARCI-M FSG GLP: Y, published: N 2309396 / ASB2012-11491	Y	ADM
KIIA 5.5.3 KIIA 5.10 (OECD)	Landgren, O., Kyle, R.A., Hoppin, J.A., Freeman, L.E.B., Cerhan, J.R., Katzmann, J.A., Rajkumar, S.V., Alavanja, M.C.	2009	Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study Blood 113, 6386-6391 GLP: N, published: Y 2309874 / ASB2012-11875	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Langridge, P.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 441 ASB2013-10986	N	---

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KIIA 5.5.3 KIIA 5.10 (OECD)	Lash, T.L.	2007	Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty J Occup Med Toxicol 2, 1-9 GLP: N, published: Y 2309876 / ASB2012-11877	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Lee, W.J., Lijinsky, W., Heineman, E.F., Markin, R.S., Weisenburger, D.D., Ward, M.H.	2004	Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus Occupational and Environmental Medicine 61 (9):743-749 61, 743-749 GLP: N, published: Y 2309888 / ASB2012-11883	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Lee, W.J., Colt, J.S., Heineman, E.F., McComb, R., Weisenburger, D.D., Lijinsky, W., Ward, M.H.	2005	Agricultural pesticide use and risk of glioma in Nebraska, United States Occupational and Environmental Medicine 62, 786-792 GLP: N, published: Y 2309886 / ASB2012-11882	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Monge, P., Wesseling, C., Guardado, J., Lundberg, I., Ahlbom, A., Cantor, K.P., Weideroass, E., Partanen, T.	2007	Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa Rica Scandinavian Journal of Work Environment & Health 33, 293-303 GLP: N, published: Y 2309948 / ASB2012-11909	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Multigner, L., Ndong, J.R., Oliva, A., Blanchet, P.	2008	Environmental pollutants and prostate cancer: epidemiological data Gynecol Obstet Fertil 36, 848-856 GLP: N, published: Y 2309964 / ASB2012-11917	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Ndong, J.R., Blanchet, P., Multigner, L.	2009	Pesticides and prostate cancer: epidemiological data Bulletin Du Cancer 96, 171-180 GLP: N, published: Y 2309974 / ASB2012-11922	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Nordström, M.; Hardell, L.; Magnuson, A.; Hagberg, H.; Rask-Andersen, A.	1998	Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study TOX1999-687	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Ollivier, L.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 458 ASB2013-11000	N	---

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KIIA 5.5.3 KIIA 5.10 (OECD)	Pahwa, P., Karunanayake, C.P., Dosman, J.A., Spinelli, J.J., McDuffie, H.H., McLaughlin, J.R.	2011	Multiple Myeloma and Exposure to Pesticides: A Canadian Case-Control Study Journal of Agromedicine 17, 40-50 GLP: N, published: Y 2309996 / ASB2012-11987	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Panchin, A. Y.;	2013	Toxicity of roundup-tolerant genetically modified maize is not supported by statistical tests Food and Chemical Toxicology 53 (2013) 475 ASB2013-10937	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Pilu, R.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 454 ASB2013-10992	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	De Roos, A.J., Blair, A., Rusiecki, J.A., Hoppin, J.A., Svec, M., Dosemeci, M., Sandler, D.P., Alavanja, M.C.	2005	Cancer incidence among glyphosate-exposed pesticide applicators in the agricultural health study Environmental Health Perspectives 113, 49-54 GLP: N, published: Y 2309704 / ASB2012-11605	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	De Roos, A.J., Zahm, S.H., Cantor, K.P., Weisenburger, D.D., Holmes, F.F., Burmeister, L.F., Blair, A.	2003	Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men Occupational and Environmental Medicine 60 GLP: N, published: Y 2309706 / ASB2012-11606	N	LIT
KIIA 5.5.3 KIIA 5.10 (OECD)	Schorsch, F.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 465–466 ASB2013-10996	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Séralini, G.-E.; Clair, E.; Mesnage, R.; Gress, S.; Defarge, N.; Malatesta, M.; Hennequin, D.; Spiroux de Vendômois, J.;	2012	Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Food and Chem Toxicol., in Press, ASB2012-15514	N	---

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KIIA 5.5.3 KIIA 5.10 (OECD)	Séralini, G. E.; Mesnage, R.; Defarge, N.; Gress, S.; Hennequin, D.; Clair, E.; Malatesta, M.; Spiroux de Vendômois, J.;	2013	Answers to critics: Why there is a long term toxicity due to a Rounduptolerant genetically modified maize and to a Roundup herbicide Food and Chemical Toxicology 53 (2013) 476–483 ASB2013-10985	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	de Souza, L.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 440 ASB2013-10999	N	---
KIIA 5.5.3 (OECD)	Sugimoto, K.	1997	HR-001: 18-Month Oral Oncogenicity Study in Mice IET 940151 ALS GLP: Y, published: N 2309415 / ASB2012-11493	Y	ALS
KIIA 5.5.3 KIIA 5.10 (OECD)	Tester, M.;	2012	Letter to the Editor Food and Chemical Toxicology 53 (2013) 457 ASB2013-10994	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Tien, D. L.; Huy, H. L.;	2012	Comments on ''Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize'' Food and Chemical Toxicology 53 (2013) 443–444 ASB2013-10984	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Trewavas, A.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 449 ASB2013-10989	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Tribe, D.;	2012	Letter to the editor Food and Chemical Toxicology 53 (2013) 467–472 ASB2013-10997	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Wager, R.;	2013	Letter to the editor Food and Chemical Toxicology 53 (2013) 455–456 ASB2013-10993	N	---
KIIA 5.5.3 KIIA 5.10 (OECD)	Weichenthal, S., Moase, C., Chan, P.	2010	A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort Environ Health Perspect 118, 1117-1125 GLP: N, published: Y 2310122 / ASB2012-12048	N	LIT

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KIIA 5.5.3 (OECD)	Wood, E., Dunster, J., Watson, P., Brooks, P.	2009	Glyphosate Technical: Dietary carcinogenicity study in the mouse SPL 2060-0011 NUF GLP: Y, published: N 2309412 / ASB2012-11492	Y	NUF
KIIA 5.6.1 (OECD)	Antal, A.	1985	Three-generation reproduction study in rats with the oral administration of glyphosate TOX9650161	N	---
KIIA 5.6.1 (OECD)	Bhide, M. B.	1988	Report on effect of glyphosate technical of Excel Industries Ltd., Bombay, on fertility and general reproductive performance (Segment I) TOX9551832	N	---
KIIA 5.6.1 (OECD)	Bhide, M. B.	1988	Report on effect of pesticides on reproductive process - Segment IV - three generation reproduction study with albino rats using glyphosate technical of Excel Industries Ltd., Bombay TOX9551965	N	---
KIIA 5.6.1 (OECD)	Brooker, A. J.; Homan, B. A.; Hadley, J. C.; Offer, J. M.	1991	Dietary range finding study of glyphosate in pregnant rats and their juvenile offspring CHV 42/90619 TOX9552388	N	---
KIIA 5.6.1 (OECD)	Brooker, A.J., Myers, D.P., Parker, C.A., Offer, J.M., Singh, H., Anderson, A., Dawe, I.S.	1992	The Effect of Dietary Administration of Glyphosate on Reproductive Function of Two Generations in the Rat CHV 47/911129 CHE GLP: Y, published: N 2309436 / TOX9552389	N	CHE
KIIA 5.6.1 (OECD)	Dhinsa, N.K., Watson, P., Brooks, P.N	2007	Glyphosate technical: Dietary Two Generation Reproduction Study in the Rat 2060/0013 NUF GLP: Y, published: N 2309418 / ASB2012-11494	Y	NUF
KIIA 5.6.1 (OECD)	Moxon, M.E.	2000	Glyphosate acid: Multigeneration reproduction toxicity study in rats CTL/P/6332 SYN / MON GLP: Y, published: N 2309423 / TOX2000-2000	Y	SYN
KIIA 5.6.1 (OECD)	Reyna, M.S.	1990	Two Generation Reproduction Feeding Study with Glyphosate in Sprague-Dawley Rats MSL-10387 MON GLP: Y, published: N 2309439 / ASB2012-11496 / TOX9552387	N	MON

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KIIA 5.6.1 (OECD)	Suresh, T.P.	1993	Two Generation Reproduction Study in Wistar Rats TOXI: 885-RP-G2 GLP: Y, published: N 2309427 / TOX9300009 / TOX9551104	N	ADM
KIIA 5.6.1 (OECD)	Takahashi, K.	1997	HR-001: A two-generation reproduction study in rats IET 96-0031 ALS GLP: Y, published: N 2309425 / ASB2012-11495	N	ALS
KIIA 5.6.10 (OECD	Antoniou, M.; Habib, M.E.M; Howard, C.V.; Jennings, R.C.; Leifert, C.; Nodari, R.O.; Robinson, C.J.; Fagan, J.	2012	Teratogenic Effects of Glyphosate-Based Herbicides: Divergence of Regulatory Decisions from Scientific Evidence J Environ Anal Toxicol 2012, S:4, ASB2012-15927	N	---
KIIA 5.6.10 (OECD)	Brooker, A. J.; John, D. M.; Anderson, A.; Dawe, I. S.	1991	The effect of glyphosate on pregnancy of the rat (incorporates preliminary investigation) CHV 43 u. 41/90716 TOX9552393	N	---
KIIA 5.6.10 (OECD)	Hatakenaka	1995	HR-001: Teratogenicity Study in Rats IET 94-0152 ALS GLP: Y, published: N 2309444 / ASB2012-11497	Y	ALS
KIIA 5.6.10 (OECD)	Mesnage, R.; Bernay, B.; Séralini, G.-E.	2012	Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity Toxicology, in Press ASB2012-13917	N	---
KIIA 5.6.10 (OECD)	Moxon, M. E.	2002	Amendment 001 to glyphosate acid: Developmental toxicity study in the rat CTL/P/4819 ! RR0690 ASB2012-10080	N	---
KIIA 5.6.10 (OECD)	Suresh, T. P.	1991	Glyphosate techn. (FSG 03090 H/05 March 1990): Teratogenicity study in Wistar rats ES.883.TER-R ! TOXI-883/1991 ! ES-GPT-TER-R TOX9551105	N	---
KIIA 5.6.10 (OECD)	Tasker, E. J.; Rodwell, D. E.; Jessup, D. C.	1980	Glyphosate: Teratology study in rats 401-054 ! IR-79-016 TOX9552392	N	---

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KIIA 5.6.11 (OECD)	Bailey, J.; Hauswirth, J.; Stump, D.;	2013	No evidence of endocrine disruption by glyphosate in male and female pubertal assays. Abstract ASB2013-3464	N	---
KIIA 5.6.11 (OECD)	Bhide, M.B., Patil, U.M.	1989	Rabbit Teratology Study with Glyphosate Technical IIT Project No. 1086 EXC GLP: Y, published: N 2309462 / TOX9551960	N	EXC
KIIA 5.6.11 (OECD)	Brooker, A.J., Brennan, C., John, D.M., Anderson, A., Dawe, I.S.	1991	The Effect of Glyphosate on Pregnancy of the Rabbit (Incorporates Preliminary Investigations) CHV 45 & 39 & 40/901 CHE GLP: Y, published: N 2309454 / TOX9552391	N	CHE
KIIA 5.6.11 (OECD)	Coles, R.J., Doleman, N.	1996	Glyphosate technical: Oral gavage teratology study in the rabbit 434/020 NUF GLP: Y, published: N 2309448 / ASB2012-11499	Y	NUF
KIIA 5.6.11 (OECD)	Hojo, H.	1995	HR-001: A Teratogenicity Study in Rabbits IET 94-0153 ALS GLP: Y, published: N 2309446 / ASB2012-11498	N	ALS
KIIA 5.6.11 (OECD)	Kimmel, G.L.; Kimmel, C.A.; Williams, A.L.; DeSesso, J.M.;	2013	Evaluation of developmental toxicity studies of glyphosate with attention to cardiovascular development Critical Reviews in Toxicology 43(2013)2: 79-95, ASB2013-3462	N	---
KIIA 5.6.11 (OECD)	Moxon, M.E.	1996	Glyphosate acid: Developmental toxicity study in the rabbit CTL/P/5009 SYN GLP: Y, published: N 2309450 / TOX2000-2002	N	SYN
KIIA 5.6.11 (OECD)	Suresh, T.P.	1993	Teratogenicity study in rabbits - Tets compound: Glyphosate technical TOXI: 884-TER-RB GLP: Y, published: N 2309457 / TOX9551106	N	ADM
KIIA 5.6.11 (OECD)	Tasker, E.J., Rodwell, D.E., Jessup, D.C.	1980	Technical Glyphosate: Teratology study in rabbits IR-79-018 MON GLP: N, published: N 2309452 / TOX9552390	N	MON

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KIIA 5.6.2 (OECD)	Moxon, M. E.	1996	Glyphosate acid: Developmental toxicity study in the rat 29.03.1996 CTL/P/4819 ! RR 0690 TOX2000-2001	N	---
KIIA 5.6.2 (OECD)	Wood, E.	2011	Glyphosate Technical: Dietary carcinogenicity study in the mouse – Amendment SPL 2060-0011 ASB2014-9149		
KIIA 5.6.2 (OECD)	Wood, E.	2011	Assessment and further discussion on relevance of perceived elevation in testicular atrophy for SafePharm project number 2060/0011 (Glyphosate technical: mouse oncogenicity study) SPL 2060-0011 ASB2014-9150		
KIIA 5.7. (OECD	Johnson, A. J.	1996	Glyphosat Acid: Acute delayed neurotoxicity study with in the domestic hen CTL/C/3122 ! C2.8/01 ! ISN 361 ASB2013-9828	N	---
KIIA 5.7.1 (OECD)	Horner, S.A	1996	Glyphosate acid: Acute neurotoxicity study in rats CTL/P/4866 SYN GLP: Y, published: N 2309464 / ASB2012-11500	N	SYN
KIIA 5.7.4 KIIA 5.10 (OECD)	Astiz, M., de Alaniz, M.J., Marra, C.A.	2009	Effect of pesticides on cell survival in liver and brain rat tissues Ecotoxicol Environ Saf 72, 2025-2032 GLP: N, published: Y 2309582 / ASB2012-11549	N	LIT
KIIA 5.7.4 KIIA 5.9 KIIA 5.10 (OECD)	Barbosa, E.R., da Costa, M.D.L., Bacheschi, L.A., Scaff, M., Leite, C.C.	2001	Parkinsonism after glycine-derivate exposure Movement Disorders 16, 565-568 GLP: N, published: Y 2309598 / ASB2012-11557	N	LIT
KIIA 5.7.4 KIIA 5.10 (OECD)	Cole, R.D., Anderson, G.L., Williams, P.L.	2004	The nematode Caenorhabditis elegans as a model of organophosphate-induced mammalian neurotoxicity Toxicology and Applied Pharmacology 194, 248-256 GLP: N, published: Y 2309680 / ASB2012-11594	N	LIT

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KIIA 5.7.4 KIIA 5.10 (OECD)	da Costa, M.D.L., Goncalves, L.R., Barbosa, E.R., Bacheschi, L.A.	2003	Neuroimaging abnormalities in parkinsonism: study of five cases Arquivos De Neuro-Psiquiatria 61, 381-386 GLP: N, published: Y 2309688 / ASB2012-11598	N	LIT
KIIIA 5.7.4 KIIA 5.10 (OECD)	Engel, L.S., Checkoway, H., Keifer, M.C., Seixas, N.S., Longstreth, W.T., Jr., Scott, K.C., Hudnell, K., Anger, W.K., Camicioli, R.	2001	Parkinsonism and occupational exposure to pesticides Occup Environ Med 28, 582-589 GLP: N, published: Y 2309718 / ASB2012-11612	N	LIT
KIIA 5.7.4 KIIA 5.10 (OECD)	Gui, Y.-x., Fan, X.-n., Wang, H.-m., Wang, G., Chen, S.-d.	2012	Glyphosate induced cell death through apoptotic and autophagic mechanisms Neurotoxicology and Teratology GLP: N, published: Y 2309778 / ASB2012-11835	N	LIT
KIIA 5.7.4 KIIA 5.10 (OECD)	Heu, C., Elie-Caille, C., Mougey, V., Launay, S., Nicod, L.	2012	A step further toward glyphosate-induced epidermal cell death: Involvement of mitochondrial and oxidative mechanisms Environmental Toxicology and Pharmacology 34, 144-153 GLP: N, published: Y 2309800 / ASB2012-11844	N	LIT
KIIA 5.7.4 (OECD)	Horner, S.A.	1996	Glyphosate Acid: Subchronic Neurotoxicity Study In Rats CTL/P/4867 SYN GLP: Y, published: N 2309466 / ASB2012-11501	N	SYN
KIIA 5.7.4 KIIA 5.10 (OECD)	Kamel, F., Tanner, C.M., Umbach, D.M., Hoppin, J.A., Alavanja, M.C.R., Blair, A., Comyns, K., Goldman, S.M., Korell, M., Langston, J.W., Ross G.W., Sandler, D.P.	2007	Pesticide exposure and self-reported Parkinson's disease in the agricultural health study American Journal of Epidemiology 165, 364-374 GLP: N, published: Y 2309838 / ASB2012-11862	N	LIT

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KIIA 5.7.4 KIIA 5.10 (OECD)	Mink, P.J., Mandel, J.S., Lundin, J.I., Sceurman, B.K.	2011	Epidemiologic studies of glyphosate and non-cancer health outcomes: A review Regulatory Toxicology and Pharmacology 61, 172-184 GLP: N, published: Y 2309938 / ASB2012-11904	N	LIT
KIIA 5.7.4 KIIA 5.10 (OECD)	Negga, R., Rudd, D.A., Davis, N.S., Justice, A.N., Hatfield, H.E., Valente, A.L., Fields, A.S., Fitsanakis, V.A.	2011	Exposure to Mn/Zn ethylene-bis-dithiocarbamate and glyphosate pesticides leads to neurodegeneration in Caenorhabditis elegans NeuroToxicology 32, 331-341 GLP: N, published: Y 2309976 / ASB2012-11923	N	LIT
KIIA 5.7.4 KIIA 5.9 KIIA 5.10 (OECD)	Wang, G., Fan, X.N., Tan, Y.Y., Cheng, Q., Chen, S.D.	2011	Parkinsonism after chronic occupational exposure to glyphosate Parkinsonism & Related Disorders 17, 486-487 GLP: N, published: Y 2310120 / ASB2012-12047	N	LIT
KIIA 5.8 (OECD)	Akanuma, M.	1996	AMPA, Reverse Mutation Test IET 96-0076 ALS GLP: Y, published: N 2309478 / ASB2012-11507	Y	ALS
KIIA 5.9 (OECD)	Bakke, J. P.	1991	Evaluation of the potential of AMPA to induce unscheduled DNA synthesis in the in vitro hepatocyte DNA repair assay using the male F-344 rats 2495-V01-91 ! SR-91-234 TOX9552409	N	---
KIIA 5.8 (OECD)	Callander, R.D.	1988	Aminomethyl Phosphonic Acid: An Evaluation of Mutagenic Potential Using *S. typhimurium* and *E. coli* CTL/P/2206 SYN GLP: Y, published: N 2309476 / TOX9500043	N	SYN
KIIA 5.8 (OECD)	Cuthbert, J. A.; Jackson, D.	1993	AMPA: Acute oral toxicity (limit) test in rats 8763 ! IRI 552409 TOX9552395	N	---
KIIA 5.8 (OECD)	Cuthbert, J. A.; Jackson, D.	1993	AMPA: Acute dermal toxicity (limit) test in rats 8764 ! IRI 552409 TOX9552396	N	---
KIIA 5.8 (OECD)	Cuthbert, J. A.; Jackson, D.	1993	AMPA: Magnusson-Kligman maximisation test in guinea pigs 8765 ! IRI 552409 TOX9300374	N	---

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KIIA 5.8 (OECD)	Estes, F. L.; Jefferson, N. D.; Blair, M.; Goldenthal, E. I.	1979	CP 50435: 90-day subacute rat toxicity study 401-050 ! IRD-78-174 TOX9552401	N	---
KIIA 5.8 (OECD)	Hazelden, K. P.	1992	AMPA: Teratogenicity study in rats 7891 ! IRI 490421 TOX9300348	N	---
KIIA 5.8 (OECD)	Heath, J.; Strutt, A.; Iswariah, V.	1993	AMPA: 4 week dose range finding study in rats with administration by gavage 7803 ! IRI 450860 TOX9300349	N	---
KIIA 5.8 (OECD)	Holson, J. F.	1991	A developmental toxicity study of AMPA in rats WIL-50159 ! WI-90-266 TOX9552414	N	---
KIIA 5.8 (OECD)	Jacobsen, S. D.; Skydsgaard, K.	1991	Assessment of acute oral toxicity of (N-methyl-N-phosphonomethyl)glycine to rats 12837 TOX9552398	N	---
KIIA 5.8 (OECD)	Jensen, J. C.	1993	Mutagenicity test: Ames salmonella test with AMPA, batch 286-JRJ-73-4, 13269 TOX9300378	N	---
KIIA 5.8 (OECD)	Jensen, J. C.	1993	AMPA, batch 286-JRJ-73-4: Mutagenicity test: *In vitro* mammalian cell gene mutation test performed with mouse lymphoma cells (L5178Y) 13270 TOX9300380	N	---
KIIA 5.8 (OECD)	Jensen, J. C.	1993	Mutagenicity test: Micronucleus test with AMPA, batch 286-JRJ-73-4 13268 TOX9300379	N	---
KIIA 5.8 (OECD)	Kier, L. D.; Stegeman, S. D.	1993	Mouse micronucleus study of AMPA EHL-90170/ML-90-404 ! MSL 13243 TOX9552413	N	---
KIIA 5.8 (OECD)	Komura, H.	1996	AMPA: Acute Oral Toxicity Study In Mice IET 96-0075 ALS GLP: Y, published: N 2309468 / ASB2012-11502	Y	ALS
KIIA 5.8 (OECD)	Leah, A.M.	1988	Aminomethyl Phosphonic Acid: Acute Oral Toxicity to the Rat CTL/P/2266 SYN GLP: Y, published: N 2309470 / TOX9500044	N	SYN

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KIIA 5.8 (OECD)	Leuschner, J.	2002	Acute Toxicity Study of AMPA (Aminomethyl Phosphonic Acid) in CD Rats by Dermal Administration - LIMIT TEST 16168/02 GLP: Y, published: N 2309472 / ASB2012-11503	Y	ADM
KIIA 5.8 (OECD)	Leuschner, J.	2002	Examination of AMPA (Aminomethyl Phosphonic Acid) in the Skin Sensitisation Test in Guinea Pigs according to Magnusson And Kligman (Maximisation Test) 16169/02 GLP: Y, published: N 2309474 / ASB2012-11506	Y	ADM
KIIA 5.8 (OECD)	Nesslany, F.	2002	Measurement of unscheduled DNA synthesis (UDS) in rat hepatocytes in vitro procedure with AMPA (Amino methyl phosphonic acid) IPL-R 020625 ALS GLP: Y, published: N 2309480 / ASB2012-11508	Y	ALS
KIIA 5.8 (OECD)	Strutt, A. V.; Atkinson, C.; Hudson, P.; Snodgrass, E.	1993	AMPA: 13-week toxicity study in rats with administration by gavage 7866 ! IRI 450876 TOX9300377	N	---
KIIA 5.8 (OECD)	Tompkins, E. C.	1991	90-day oral (capsule) toxicity study in dogs with AMPA WIL-50173 ! WI-90-354 TOX9552406	N	---
KIIA 5.9 (OECD)	Acquavella, J.F., Weber, J.A., Cullen, M.R., Cruz, O.A., Martens, M.A., Holden, L.R., Riordan, S., Thompsen, M., Farmer, D.	1999	Human ocular effects from self-reported exposures to Round-up herbicides Human & Experimental Toxicology (paper) 18, 479-486 GLP: N, published: Y 2309482 / TOX2002-699	N	LIT
KIIA 5.9 (OECD)	Bando, H., Murao, Y., Aoyagi, U., Hirakawa, A., Iwase, M., Nakatani, T.	2010	[Extreme hyperkalemia in a patient with a new glyphosate potassium herbicide poisoning: report of a case] Chudoku Kenkyu 23, 246-249 GLP: N, published: Y 2309596 / ASB2012-11556	N	LIT
KIIA 5.9 (OECD)	BfR	2011	Frauenmilch: Dioxingehalte sinken kontinuier-lich. Information Nr. 011/2011 des BfR vom 23.03.2011 ASB2014-8171	N	---

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KIIA 5.9 KIIIA1 7.6.3 (OECD)	Bradberry, S.M., Proutfoot, A.T., Vale, J.A.	2004	Glyphosate poisoning Toxicological reviews (paper), 23, 159-167 GLP: N, published: Y 2309484 / ASB2012-11509	N	LIT
KIIA 5.9 (OECD)	Bradberry, S.M., Proudfoot, A.T., Vale, J.A.	2004	Glyphosate poisoning Toxicol Rev 23, 159-167 GLP: N, published: Y 2309642 / ASB2012-11576	N	LIT
KIIA 5.9 (OECD)	Burger, R.; Begemann, K.; Meyer, H.; Hahn, A.;	2009	Severe dyspnoea after spraying of a pesticide containing glyphosate. Lung damage histologically confirmed Clinical Toxicology (2009) 47, 506 ASB2013-11831	N	---
KIIA 5.9 (OECD)	Chang, C.-J., Peng, Y.-C., Hung, W.-H., Yang, D.-Y., Lin, T.-J.	1999	Clinical impact of upper gastrointestinal tract injuries in glyphosate-surfactant oral intoxication Human & Experimental Toxicology (paper), 18, 475-478 GLP: N, published: Y 2309486 / ASB2012-11510	N	LIT
KIIA 5.9 (OECD)	Fromme, H.; Gruber, L.; Seckin, E.; et al.;	2011	Phthalates and their metabolites in breast milk — Results from the Bavarian Monitoring of Breast Milk (BAMBI) Environment International 37 (2011) 715–722 ASB2014-8169	N	LIT
KIIA 5.9 (OECD)	Fürst, P.	2006	Dioxins, polychlorinated biphenyls and other organohalogen compounds in human milk Mol. Nutr. Food Res. 2006, 50, 922 – 933 ASB2014-8168	N	LIT
KIIA 5.9 (OECD)	Goldstein, D.A., Johnson, G., Farmer, D.R., Martens, M.A.	1999	Pneumonitis and herbicide exposure Chest (paper), 16, 1139-1140 GLP: N, published: Y 2309490 / ASB2012-11511	N	LIT
KIIA 5.9 (OECD)	Goldstein, D.A., Acquavella, J.F., Mannion, R.M., Farmer, D.R.	2002	An analysis of glyphosate data from the California Environmental Protection Agency Pesticide Illness Surveillance Program Journal of Toxicology-Clinical Toxicology 40, 885-892 GLP: N, published: Y 2309770 / ASB2012-11831	N	LIT
KIIA 5.9 (OECD)	Kamijo, Y., Mekari, M., Yoshimura, K., Kano, T., Soma, K.	2012	Glyphosate-surfactant herbicide products containing glyphosate potassium salt can cause fatal hyperkalemia if ingested in massive amounts Clinical Toxicology 50, 159 GLP: N, published: Y 2309840 / ASB2012-11863	N	LIT

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KIIA 5.9 (OECD)	Lee, H-L., Chen, K.-W., Chi, C.-H., Huang, J.-J., Tsai, L.-M.	2000	Clinical presentations and prognostic factors of a glyphosate-surfactant herbicide intoxication: a review of 131 cases Academic Emergency Medicine (paper) 7, 906-910 GLP: N, published: Y 2309492 / ASB2012-11512	N	LIT
KIIA 5.9 (OECD)	Lee, C.H., Shih, C.P., Hsu, K.H., Hung, D.Z., Lin, C.C.	2008	The early prognostic factors of glyphosate-surfactant intoxication Am J Emerg Med 26, 275-281 GLP: N, published: Y 2309880 / ASB2012-11879	N	LIT
KIIA 5.9 KIIA 5.10 KIIIA1 7.6.3 (OECD)	Mizuyama, K.	1987	Irritating effect of glyphosate, surfactant and roundup on stomach and small intestine in dogs MON GLP: N, published: N 2309496 / TOX9552430	N	MON
KIIA 5.9 (OECD)	Paumgartten, F.J.R.	2012	ANVISA - Glyphosate Intoxications 2010 to 2012 in Brasil; ASB2013-13413	N	---
KIIA 5.9 (OECD)	Pushnoy, L.A., Avnon, L.S., Carel, R.S.	1998	Herbicide (Roundup) Pneumonitis Chest (paper), 114, 1769-1771 GLP: N, published: Y 2309498 / ASB2012-11513	N	LIT
KIIA 5.9 (OECD)	Raab, U.; Albrecht, M.; Preiss, U.; et al.;	2013	Organochlorine compounds, nitro musks and perfluorinated substances in breast milk – Results from Bavarian Monitoring of Breast Milk 2007/8 Chemosphere 93 (2013) 461–467 ASB2014-8170	N	LIT
KIIA 5.9 (OECD)	Sawada, Y., Nagai, Y., Ueyama, M., Yamamoto, I.	1988	Probable toxicity of surface-active agent in commercial herbicide containing glyphosate The Lancet (paper) 1, 299-301 GLP: N, published: Y 2309504 / Z35532	N	LIT
KIIA 5.9 (OECD)	Tominack, R., Conner, P., Yamashita, M.	1989	Clinical Management of Roundup® herbicide exposure The Japanese Journal of Toxicology (paper) 2, 187-192 GLP: N, published: Y 2309506 / TOX9552426	N	LIT

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KIIA 5.9 (OECD)	UBA	2008	Aktualisierung der Referenzwerte für HCB, β-HCH, DDT und PCB in Frauenmilch. Stellungnahme der Kommission Human-Biomonitoring des Umweltbundesamtes *BfR Stillkommission* Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz 2008 · 51:1239–1242 ASB2014-8167	N	---
KIIA 5.9 (OECD)	Verdugo-Raab, U.;	2012	Ergebnisse der Muttermilchuntersuchungen 1984–2010 Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit ASB2014-8173	N	---
KIIA 5.10 (OECD)	AFSSA	2009	Avis de l'Agence française de sécurité sanitaire des aliments relatif au glyphosate et aux préparations phytopharmaceutiques à base de cette substance active GLP: N, published: Y 2309546 / ASB2012-11532	N	LIT
KIIA 5.10 (OECD)	Allen, S.L.	1996	Glyphosate Acid: Comparison of Salivary Gland Effects in Three Strains of Rat CTL/P/5160 SYN GLP: Y, published: N 2309518 / ASB2012-11520	N	SYN
KIIA 5.10 (OECD)	Allen, S.L.	1996	Glyphosate Acid: Comparison of Salivary Gland Effects in Three Strains of Rat CTL/P/5160 SYN GLP: Y, published: N 2309558 / ASB2012-11537	Y	MOD
KIIA 5.10 (OECD)	Alavanja, M. C. R.; Ross, M. K.; Bonner, M. R.	2013	Increased cancer burden among pesticide applicators and others due to pesticide exposure CA: A Cancer Journal for Clinicians, 2013;63:120–142 ASB2014-9174	N	LIT
KIIA 5.10 (OECD)	Alavanja, M. C. R.; Bonner, M. R.	2012	Occupational pesticide exposures and cancer risk: a review Journal of Toxicology and Environmental Health, Part B, 15:238–263, 2012 ASB2014-9173	N	LIT
KIIA 5.10 (OECD)	Alvarez-Moya, C.; Reynoso Silva, M.; Valdez Ramírez, C.; et al.;	2014	Comparison of the in vivo and in vitro genotoxicity of Glyphosate Isopropylamine salt in three different organisms Genetics and Molecular Biology, 37, 1, 105-110 (2014) ASB2014-6902	N	LIT

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KIIA 5.10 (OECD)	Altenburger, R.; Scholz, S.; Schmitt-Jansen, M.; Busch, W.; Escher B. I.	2012	Mixture toxicity revisited from a toxicogenomic perspective Environ. Sci. Technol. 2012, 46, 2508−2522 ASB2014-9176	N	LIT
KIIA 5.10 (OECD)	Andreotti, G.; Koutros, S.; Berndt, S. I. et al.	2012	The Interaction between pesticide use and genetic variants involved in lipid metabolism on prostate cancer risk Journal of Cancer Epidemiology Volume 2012, Article ID 358076, ASB2014-9198	N	LIT
KIIA 5.10 (OECD)	Anonymous	2009	Final List of Initial Pesticide Active Ingredients and Pesticide Inert Ingredients to be Screened Under the Federal Food, Drug, and Cosmetic Act Federal Register /Vol. 74, No. 71 /Wednesday, April 15, 2009 /Notices, 17579-17585 74, 17579-17585 GLP: N, published: Y 2310108 / ASB2012-12041	N	LIT
KIIA 5.10 (OECD)	Anonymous	2012	GM Soy linked to health damage in pigs -- a Danish Dossier ASB2013-11007	N	---
KIIA 5.10 (OECD)	Anonymous	2013	Effects on ruminants and other herbivores (livestock and wild life) ASB2013-11007	N	---
KIIA 5.10 (OECD)	Antoniou, M.; Brack, P.; Carrasco, A. et al.	2010	GV-SOYA - Nachhaltig? - Verantwortungsbewusst? - Zusammenfassung der wichtigsten Ergebnisse ASB2012-803	N	---
KIIA 5.10 (OECD)	Arbuckle, T.E., Lin, Z.Q., Mery, L.S.	2001	An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population Environmental Health Perspectives 109, 851-857 GLP: N, published: Y 2309574 / ASB2012-11545	N	LIT
KIIA 5.10 (OECD)	Aris, A., Leblanc, S.	2011	Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada Reproductive Toxicology 31, 528-533 GLP: N, published: Y 2309578 / ASB2012-11547	N	LIT

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KIIA 5.10 (OECD)	Astiz, M.; de Catalfo, G.; Garcia, M.	2013	Pesticide-induced decrease in rat testicular steroidogenesisis differentially prevented by lipoate and tocopherol Ecotoxicology and Environmental Safety 91 (2013) 129–138 ASB2014-7493	N	LIT
KIIA 5.10 (OECD)	Astiz, M.; de Alaniz, M. J. T.; Marra, C. A.	2012	The oxidative damage and inflammation caused by pesticides are reverted by lipoic acid in rat brain Neurochemistry International 61 (2012) 1231–1241 ASB2014-9201	N	LIT
KIIA 5.10 (OECD)	Axelrad, J.C., Howard, C.V., McLean, W.G.	2003	The effects of acute pesticide exposure on neuroblastoma cells chronically exposed to diazinon Toxicology 185, 67-78 GLP: N, published: Y 2309590 / ASB2012-11553	N	LIT
KIIA 5.10 (OECD)	Bailey, J.; Hauswirth, J.; Stump, D.;	2013	No evidence of endocrine disruption by glyphosate in male and female pubertal assays. Abstract SOT 2013 Annual Meeting, PS 1937: p 412 ASB2013-3464	N	---
KIIA 5.10 (OECD)	Basrur, P. K.;	2006	Disrupted sex differentiation and feminization of man and domestic animals Environmental Research 100 (2006) 18–38 ASB2014-7492	N	LIT
KIIA 5.10 (OECD)	Bates, N.; Ed-wards, N.	2013	Letter to the editor: Glyphosate toxicity in animals Clinical Toxicology (2013), 51, 1243 ASB2014-9249	N	LIT
KIIA 5.10 (OECD)	Bell, E.M., Hertz-Picciotto, I., Beaumont, J.J.	2001	A case-control study of pesticides and fetal death due to congenital anomalies Epidemiology 12, 148-156 GLP: N, published: Y 2309602 / ASB2012-11559	N	LIT
KIIA 5.10 (OECD)	Belle, R., Le Bouffant, R., Morales, J., Cosson, B., Cormier, P., Mulner-Lorillon, O.	2007	Sea urchin embryo, DNA-damaged cell cycle checkpoint and the mechanisms initiating cancer development J Soc Biol 201, 317-327 GLP: N, published: Y 2309604 / ASB2012-11560	N	LIT

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KIIA 5.10 (OECD)	Bellé, R.; Morales, J.; Cormier, P.; Mulner-Lorillon, O.	2012	Letter to the editor: Toxicity of Roundup and Glyphosate Journal of Toxicology and Environmental Health, Part B, 15:233–237, 2012 ASB2014-9251	N	LIT
KIIA 5.10 (OECD)	Benachour, N., Sipahutar, H., Moslerni, S., Gasnier, C., Travert, C., Seralini, G.E.	2007	Time- and dose-dependent effects of roundup on human embryonic and placental cells Archives of Environmental Contamination and Toxicology 53, 126-133 GLP: N, published: Y 2309608 / ASB2009-9018	N	LIT
KIIA 5.10 (OECD)	Benedetti, A.L., Vituri, C.D., Trentin, A.G, Domingues, M.A.C., Alvarez-Silva, M.	2004	The effects of sub-chronic exposure of Wistar rats to the herbicide Glyphosate-Biocarb (R) Toxicology Letters 153, 227-232 GLP: N, published: Y 2309610 / ASB2012-11562	N	LIT
KIIA 5.10 (OECD)	Benitez-Leite, S., Macchi, M., Acosta, M.	2009	Malformaciones congénitas asociadas a agrotóxicos Archives of Pediatrics 80 (3):377-378. 80, 377-378 GLP: N, published: Y 2309612 / ASB2012-11563	N	LIT
KIIA 5.10 (OECD)	Barry, K.; Koutros, S.; Berndt, S. et al.	2011	Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk Environmental Health Perspectives, 119(2011)12 ASB2014-9247	N	LIT
KIIA 5.10 (OECD)	Benedettia, D.; Nunesa, E.; Sarmentoa, M. et al.	2013	Genetic damage in soybean workers exposed to pesticides: Evaluation with the comet and buccal micronucleus cytome assays Mutation Research 752 (2013) 28– 33 ASB2014-9279	N	LIT
KIIA 5.10 (OECD)	Beuret, C.J., Zirulnik, F., Gimenez, M.S.	2005	Effect of the herbicide glyphosate on liver lipoperoxidation in pregnant rats and their fetuses Reproductive Toxicology 19, 501-504 GLP: N, published: Y 2309614 / ASB2012-11564	N	LIT
KIIA 5.10 (OECD)	Beswick, E.; Millo, J.	2011	Fatal poisoning with Glyphosate - surfactant herbicide JICS Volume 12, Number 1, January 2011 ASB2014-9283	N	LIT

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KIIA 5.10 (OECD)	BfR	2009	BfR-Bewertung der Studie "Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines" vom 06.08.2009 GLP: N, published: Y 2309616 / ASB2012-11565	N	LIT
KIIA 5.10 (OECD)	Bhide, M. B.; Naik, P. Y.	1987	Synergism and potentiation in rats of Glyphosate (tech.) of Excel Industries Ltd., Bombay TOX9551964	N	---
KIIA 5.10 (OECD)	Blair, A., Zahm, S.H.	1993	Patterns of pesticide use among farmers: implications for epidemiologic research Epidemiology 4, 55-62 GLP: N, published: Y 2309620 / ASB2012-11567	N	LIT
KIIA 5.10 (OECD)	Bleeke, M.S., Kurtzweil, M.L., Saltmiras, D.A.	2010	Dietary Exposure Assessment of Polyoxyethylenealkylamines(POEA) Surfactants MON GLP: N, published: Y 2309622 / ASB2010-6123	N	LIT
KIIA 5.10 (OECD)	Borgert, C. J.; Baker, S. P.; Matthews, J. C.	2013	Potency matters: Thresholds govern endocrine activity Regulatory Toxicology and Pharmacology 67 (2013) 83–88 ASB2014-9292	N	LIT
KIIA 5.10 (OECD)	Brändli, D.; Reinacher, S.	2011	Herbizide im Urin Ithaka Journal 1 | 2012:1–4 ASB2012-804	N	LIT
KIIA 5.10 (OECD)	BVL	2010	Glyphosate - Comments from Germany on the paper by Paganelli, A. et al. (2010): "Glyphosate-based Herbicides Produce Teratogenic Effects on Vertebrates by Impairing Retinoic Acid Signaling" GLP: N, published: Y 2309648 / ASB2012-11579	N	LIT
KIIA 5.10 (OECD)	Caglar, S., Kolankaya, D.	2008	The effect of sub-acute and sub-chronic exposure of rats to the glyphosate-based herbicide Roundup Environmental Toxicology and Pharmacology 25 (2008) 57–62 ASB2012-11580	N	LIT
KIIA 5.10 (OECD)	Campaña, H.; Pawluk, M. S.; López Camelo, J. S.; Grupo de Estudio del ECLAMC	2010	Prevalencia al nacimiento de 27 anomalías congénitas seleccionadas, en 7 regiones geográficas de la Argentina. Births prevalence of 27 selected congenital anomalies in 7 geographic regions of Argentina Arch Argent Pediatr 2010;108(5):409-417 ASB2013-10559	N	---

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KIIA 5.10 (OECD)	Campo, N. B.-C.; Zarate, D. H. V.; Hernandez, E. D. R.	2009	Toxicity of the main pesticides used in Popayán Valley with Bacillus subtillis Facultad de Ciencias Agropecuarias 16 Vol 7 No. 1 Enero - Junio 2009 ASB2014-9281	N	---
KIIA 5.10 (OECD)	Carmichael, S. L.; Yang, W.; Roberts, E. M. et al.	2013	Hypospadias and residential proximity to pesticide applications Pediatrics 2013;132(5)e1216–e1226 ASB2014-9307	N	LIT
KIIA 5.10 (OECD)	Carroll, R.; Metcalfe, C.; Gunnell, D. et al.	2012	Diurnal variation in probability of death following self-poisoning in Sri Lanka—evidence for chronotoxicity in humans International Journal of Epidemiology 2012;41:1821–182 ASB2014-9308	N	LIT
KIIA 5.10 (OECD)	Cassault-Meyer, E.; Gress, S.; Seralini, G. E.; Galeraud-Denis, I.;	2014	An acute exposure to glyphosate-based herbicide alters aromatase levels in testis and sperm nuclear quality Environ Toxicol. Pharmacol 38 (2014) 131–140 ASB2014-5615	N	LIT
KIIA 5.10 (OECD)	Cattani, D.; de Liz Oliveira Cavalli, V. L.; Heinz Rieg, C. E. et al.	2014	Mechanisms underlying the neurotoxicity induced by Glyphosate-based herbicide in immature rat hippocampus: Involvement of glutamate excitotoxicity Toxicology 320 (2014) 34–45 ASB2014-3919	N	LIT
KIIA 5.10 (OECD)	Chaufan, G.; Coalova, I.; Molina, M.	2014	Glyphosate commercial formulation causes cytotoxicity, oxidative effects, and apoptosis on human cells: Differences with its active ingredient International Journal of Toxicology 2014, Vol. 33(1) 29-38 ASB2014-9314 / ASB2014-7616	N	LIT
KIIA 5.10 (OECD)	Chen, Y. J.; Wu, M.-L.; Deng, J.-F.; Yang, C.-C.	2009	The epidemiology of Glyphosate-surfactant herbicide poisoning in Taiwan, 1986–2007: a poison center study Clinical Toxicology (2009) 47, 670–677 ASB2014-9318	N	LIT
KIIA 5.10 (OECD)	Chen, H.-H.; Lin, J.-L.; Huang, W-H. et al.	2013	Spectrum of corrosive esophageal injury after intentional paraquat or Glyphosate-surfactant herbicide ingestion International Journal of General Medicine 2013:6 677–683 ASB2014-9321	N	LIT

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KIIA 5.10 (OECD)	Chien, W.-C.; Chung, C.-H.; Jaakkola, J. J. K. et al.	2012	Risk and prognostic factors of inpatient mortality associated with unintentional insecticide and herbicide poisonings: A retrospective cohort study PLOS one September 2012 Volume 7 Issue 9 e45627 ASB2014-9326	N	LIT
KIIA 5.10 (OECD)	Chorfa, A.; Bétemps, D.; Morignat, E. et al.	2013	Specific pesticide-dependent increases in alpha-synuclein levels in human neuroblastoma (SH-SY5Y) and melanoma (SK-MEL-2) cell lines Toxicological Sciences 133(2), 289–297 2013 ASB2014-9328	N	LIT
KIIA 5.10 (OECD)	Clair, E., Linn, L., Travert, C., Amiel, C., Seralini, G.-E., Panoff, J.-M.	2012	Effects of Roundup and Glyphosate on Three Food Microorganisms: Geotrichum candidum, Lactococcus lactis subsp. cremoris and Lactobacillus delbrueckii subsp. bulgaricus Current Microbiology 64, 486-491 GLP: N, published: Y 2309674 / ASB2012-11592	N	LIT
KIIA 5.10 (OECD)	Clair, E., Mesnage, R., Travert, C., Séralini, G.-E.	2012	A glyphosate-based herbicide induces necrosis and apoptosis in mature rat testicular cells *in vitro*, and testosterone decrease at lower levels Toxicology *in Vitro* 26, 269-279 GLP: N, published: Y 2309678 / ASB2012-1628	N	LIT
KIIA 5.10 (OECD)	Coalova, I.; Ríos de Molina, M. C.; Chaufan, G.;	2014	Influence of the spray adjuvant on the toxicity effects of a Glyphosate formulation Toxicology in Vitro 28 (2014) 1306–1311 ASB2014-7615	N	LIT
KIIA 5.10 (OECD)	Cocco, P.; Satta, G.;	2014	Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study Occup Environ Med 2012;0:1–7 ASB2014-7523	N	LIT
KIIA 5.10 (OECD)	Corsini, E.; Sokooti, M.; Galli, C. L.; Moretto, A.; Colosio, C.	2012	Pesticide induced immunotoxicity in humans: A comprehensive review of the existing evidence Toxicology (2012) ASB2014-9352	N	LIT
KIIA 5.10 (OECD)	Culbreth, M. E.; Harrill, J. A.; Freudenrich, T. M. et al.	2012	Comparison of chemical-induced changes in proliferation and apoptosis in human and mouse neuroprogenitor cells NeuroToxicology 33 (2012) 1499–1510 ASB2014-9355	N	LIT

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KIIA 5.10 (OECD)	Curwin, B.D., Hein, M.J., Sanderson, W.T., Striley, C., Heederik, D., Kromhout, H., Reynolds, S.J., Alavanja, M.C.	2006	Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa Ann. Occup. Hyg. 2006, 1-33 ASB2012-11597	N	LIT
KIIA 5.10 KIIIA1 7.6.3 (OECD)	Dallegrave, E., Mantese, F.D., Coelho, R.S., Pereira, J.D., Dalsenter, P.R., Langeloh, A.	2003	The teratogenic potential of the herbicide glyphosate-Roundup (R) in Wistar rats Toxicology Letters 142, 45-52 GLP: N, published: Y 2309692 / ASB2012-11600	N	LIT
KIIA 5.10 KIIIA1 7.6.3 (OECD)	Dallegrave, E., Mantese, F.D., Oliveira, R.T., Andrade, A.J.M., Dalsenter, P.R., Langeloh, A.	2007	Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats Archives of Toxicology 81, 665-673 GLP: N, published: Y 2309694 / ASB2012-2721	N	LIT
KIIA 5.10 (OECD)	de Liz Oliveira Cavalli, V. L.; Cattani, D.; Rieg, C. E. H. et al.	2013	Roundup disrupts male reproductive functions by triggering calcium-mediated cell death in rat testis and Sertoli cells FreeRadicalBiologyandMedicine65(2013)335–346 ASB2014-7495	N	LIT
KIIA 5.10 (OECD)	Daruich, J., Zirulnik, F., Gimenez, M.S.	2001	Effect of the herbicide glyphosate on enzymatic activity in pregnant rats and their fetuses Environmental Research 85, 226-231 GLP: N, published: Y 2309696 / ASB2012-11601	N	LIT
KIIA 5.10 (OECD)	Da Silva, F. R.; Kvitko, K.; Rohr, P. et al.	2014	Genotoxic assessment in tobacco farmers at different crop times Science of the Total Environment 490 (2014) 334–341 ASB2014-9358	N	LIT
KIIA 5.10 (OECD)	DeSesso, J. M.; Williams, A.	2012	Comment on ''Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression" by Romano et al. 2012 Arch Toxicol (2012) 86:1791–1793 ASB2014-9369	N	LIT

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KIIA 5.10 (OECD)	De Souza Filho, J.; Neves Sousa, C. C.; Da Silva, C. C. et al.	2013	Mutagenicity and genotoxicity in gill erythro-cyte cells of Poecilia reticulata exposed to a Glyphosate formulation Bull Environ Contam Toxicol (2013) 91:583–587 ASB2014-7617	N	LIT
KIIA 5.10 (OECD)	El-Shenawy, N.S.	2009	Oxidative stress responses of rats exposed to Roundup and its active ingredient glyphosate Environmental Toxicology and Pharmacology 28 (2009) 379–385 ASB2012-11611	N	LIT
KIIA 5.10 (OECD)	El-Zaemey, S.; Heyworth, J.	2013	Noticing pesticide spray drift from agricultural pesticide application areas and breast cancer: a case-control study Aust NZ J Public Health. 2013; Online ASB2014-9473	N	LIT
KIIA 5.10 (OECD)	European Commission	2011	Standing Committee on the Food Chain and Animal Health, Section Phytopharmaceuticals - Plant Protection Products - Legislation - 22-23 November 2010 GLP: N, published: Y 2309724 / ASB2012-11615	N	LIT
KIIA 5.10 (OECD)	Faria, N. M. X.; Fassa, A. G.; Meucci, R. D. et al.	2014	Occupational exposure to pesticides, nicotine and minor psychiatric disorders among tobacco farmers in southern Brazil NeuroToxicology (2014) in Press ASB2014-9477	N	---
KIIA 5.10 (OECD)	Folta, K.	2014	Letter to the editor Food and Chemical Toxicology: 65 (2014) 392 ASB2014-9478	N	LIT
KIIA 5.10 (OECD)	Forgacs, A.L., Ding, Q., Jaremba, R.G., Huhtaniemi, I.T., Rahman, N.A., Zacharewski, T.R.	2012	BLTK1 Murine Leydig Cells: A Novel Steroidogenic Model for Evaluating the Effects of Reproductive and Developmental Toxicants Toxicological Sciences GLP: N, published: Y 2309736 / ASB2012-11621	N	LIT
KIIA 5.10 (OECD)	Freire, C.; Koifman, S.	2012	Pesticide exposure and Parkinson's disease: Epidemiological evidence of association NeuroToxicology 33 (2012) 947–971 ASB2014-9479	N	LIT

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KIIA 5.10 (OECD)	French Committee for the Study of Toxicity	2005	Enquiry into the referral of the Committee for the Study of Toxicity by the DGAL regarding the article "Differential effects of glyphosate and Roundup on human placental cells and aromatase." Richard S., Moslemi S., Sipahutar H., Benachour GLP: N, published: Y 2309742 / ASB2009-9025	N	LIT
KIIA 5.10 (OECD)	Garlich, F. M.; Goldman, M.; Pepe, J. et al.	2014	Hemodialysis clearance of glyphosate following a life-threatening ingestion of glyphosate-surfactant herbicide Clinical Toxicology (2014), 52, 66–71 ASB2014-9480	N	LIT
KIIA 5.10 (OECD)	Garry, V.F., Harkins, M.E., Erickson, L.L., Long-Simpson, L.K., Holland, S.E., Burroughs, B.L.	2002	Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA Environmental Health Perspectives 110:441-449 110, 441-449 GLP: N, published: Y 2309750 / ASB2012-11626	N	LIT
KIIA 5.10 (OECD)	Garry, V.F., Holland, S.E., Erickson, L.L., Burroughs, B.L.	2003	Male reproductive hormones and thyroid function in pesticide applicators in the Red River Valley of Minnesota Journal of Toxicology and Environmental Health-Part A 66, 965-986 GLP: N, published: Y 2309752 / ASB2012-11627	N	LIT
KIIA 5.10 (OECD)	Gasnier, C., Benachour, N., Clair, E., Travert, C., Langlois, F., Laurant, C., Decroix-Laporte, C., Seralini, G.E.	2010	Dig1 protects against cell death provoked by glyphosate-based herbicides in human liver cell lines J Occup Med Toxicol 5 GLP: N, published: Y 2309754 / ASB2012-11628	N	LIT
KIIA 5.10 (OECD)	Gasnier, C., Dumont, C., Benachour, N., Clair, E., Chagnon, M.C., Seralini, G.E.	2009	Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines Toxicology 262, 184-191 GLP: N, published: Y 2309756 / ASB2012-11629	N	LIT

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KIIA 5.10 (OECD)	Gasnier, C., Laurant, C., Decroix-Laporte, C., Mesnage, R., Clair, E., Travert, C., Seralini, G.E.	2011	Defined plant extracts can protect human cells against combined xenobiotic effects J Occup Med Toxicol 6, 3 GLP: N, published: Y 2309758 / ASB2012-11630	N	LIT
KIIA 5.10 (OECD)	Gencer, N.; Ergün, A.; Demir, D.	2012	In vitro effects of some herbicides and fungicides on human erythrocyte carbonic anhydrase activity Fresenius Environmental Bulletin, Volume 21 - No 3. 2012 ASB2014-9481	N	LIT
KIIA 5.10 (OECD)	Gentile, N.; Manas, F.; Bosch, B.; Peralta, L.; Gorla, N.; Aiassa, D.	2012	Micronucleus assay as a biomarker of genotoxicity in the occupational exposure to agrochemicals in rural workers Bull Environ Contam Toxicol (2012) 88:816–822 ASB2014-9482	N	LIT
KIIA 5.10 (OECD)	George, J.; Shukla, Y.;	2013	Emptying of intracellular calcium pool and oxidative stress imbalance are associated with the Glyphosate-induced proliferation in human skin keratinocytes HaCaT cells ISRN Dermatology, Volume 2013, Article ID 825180 ASB2014-8034	N	LIT
KIIA 5.10 (OECD)	Gil, H. W.; Park, J. S.; Hong; S. Y.	2013	Effect of intravenous lipid emulsion in patients with acute Glyphosate intoxication Clinical Toxicology (2013), 51, 767–771 ASB2014-9488	N	LIT
KIIA 5.10 (OECD)	Glyphosat task force	2014	Response to EFSA non-confidential comment 48 (EFSA non-confidential letter page 9, in reference to public comment 2(78 ASB2014-9624	N	LIT
KIIA 5.10 (OECD)	Goldner, W. S.; Sandler, D. P.; Yu, F. et al.	2013	Hypothyroidism and pesticide use among male private pesticide applicators in the agricultural health study JOEM Volume 55, Number 10, October 2013 ASB2014-9492	N	LIT
KIIA 5.10 (OECD)	Goldstein, D. A.; Saltmiras, D. A	2014	Neurodevelopmental toxicity: still more questions than answers neurology Vol 13 July 2014 ASB2014-9493	N	LIT

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KIIA 5.10 (OECD)	Grandjean, P.; Landrigan, P. J.	2014	Neurobehavioural effects of developmental toxicity Lancet Neurol 2014; 13: 330–38 ASB2014-9494	N	LIT
KIIA 5.10 (OECD)	Greenpeace	2011	Herbicide tolerance and GM cropsfedd - Why the world should be ready to round up Glyphosate ASB2012-810	N	---
KIIA 5.10 (OECD)	Gress, S.; Lemoine, S.; Puddu, P.-E.; Seralini, G.-E.; Rouet, R.;	2014	Cardiotoxic electrophysiological effects of the herbicide Roundup in rat and rabbit ventricular myocardium in vitro Cardiovasc Toxicol ASB2014-12161	N	LIT
KIIA 5.10 (OECD)	Guilherme, S.; Santos, M. A.; Barroso, C.; et al.;	2012	Differential genotoxicity of Roundupformulation and its constituents in blood cells of fish (Anguilla anguilla): considerations on chemical interactions and DNA damaging mechanisms Ecotoxicology (2012) 21:1381–1390 ASB2014-7619	N	LIT
KIIA 5.10 (OECD)	Haas, M.C.	2010	An 8-Week Oral (Diet and Gavage) Toxicity Study of Citric Acid in Male Rats WIL-50361 GTF GLP: Y, published: N 2309782 / ASB2012-11519	Y	MOD
KIIA 5.10 (OECD)	Haas, M.C.	2012	Glyphosate - A 28-Day Oral (Dietary) Immunotoxicity Study in Female B6C3F1 Mice WIL-50393 MON GLP: Y, published: N 2309522 / ASB2012-11521	Y	EGT
KIIA 5.10 (OECD)	Harrill, J. A.; Freudenich, T. M.; Robinette, B. L.; Mundy, W. R.	2011	Comparative sensitivity of human and rat neural cultures to chemical-induced inhibition of neurite outgrowth Toxicology and Applied Pharmacology 256 (2011) 268–280 ASB2014-9558	N	LIT
KIIA 5.10 (OECD)	Hayes; A. W.	2014	Reply to letter to the editor Food and Chemical Toxicology: 65 (2014) 394–395 ASB2014-9559	N	LIT

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KIIA 5.10 (OECD)	Hecker, M., Hollert, H., Cooper, R., Vinggaard, A.M., Akahori, Y., Murphy, M., Nellemann, C., Higley, E., Newsted, J., Laskey, J., Buckalew, A.	2011	The OECD validation program of the H295R steroidogenesis assay: Phase 3. Final inter-laboratory validation study Environmental Science and Pollution Research 18, 503-515 GLP: N, published: Y 2309792 / ASB2012-11840	N	LIT
KIIA 5.10 (OECD)	Hedberg, D.; Wallin, M.;	2010	Effects of Roundup and glyphosate formulations on intracellular transport, microtubules and actin filaments in Xenopus laevis melanophores Toxicology in Vitro 24 (2010) 795–802 ASB2014-7494	N	LIT
KIIA 5.10 (OECD)	Heu, C., Berquand, A., Elie-Caille, C., Nicod, L.	2012	Glyphosate-induced stiffening of HaCaT keratinocytes, a Peak Force Tapping study on living cells Journal of structural biology 178, 1-7 GLP: N, published: Y 2309798 / ASB2012-11843	N	LIT
KIIA 5.10 (OECD)	Hinojosa, R.; Baud, F.; Marque, S.; Barreteau, H.	2013	Severe poisonings in intensive care unit: Study of announced substances in 2011 Annales Pharmaceutiques Françaises (2013) 71, 174—185 ASB2014-9566	N	LIT
KIIA 5.10 (OECD)	Hoare, A.	2014	QSAR assessment on the toxicological properties of Glyphosate and its impurities Report EE/14/002, Battelle UK Limited ASB2014-9157		
KIIA 5.10 (OECD)	Hokanson, R., Fudge, R., Chowdhary, R., Busbee, D.	2007	Alteration of estrogen-regulated gene expression in human cells induced by the agricultural and horticultural herbicide glyphosate Hum Exp Toxicol 26, 747-752 GLP: N, published: Y 2309804 / ASB2012-11846	N	LIT
KIIA 5.10 (OECD)	Honeycutt, Z.; Rowlands, H.;	2014	Glyphosate Testing Report: Findings in American Mothers' Breast Milk, Urine and Water. "Moms Across America" and "Sustainable Pulse" ASB2014-6793	N	---

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KIIA 5.10 (OECD)	Horiuchi, N.; Oguchi, S.; Nagami, H. et al.	2007	Pesticide-related dermatitis in Saku District, Japan, 1975-2000 Int. J Occup. Environ Health 2007;14:25-34 ASB2014-9570	N	LIT
KIIA 5.10 (OECD)	Hour, B. T.; Belen, C.; Zar, T. et al.	2012	Herbicide Roundup intoxication: Successful treatment with continuous renal replacement therapy The American Journal of Medicine, Vol 125, No 8, August 2012 ASB2014-9571	N	LIT
KIIA 5.10 (OECD)	Jamkhande, P. G.; Chintawar, K. D.; Chandak, P. G.	2014	Teratogenicity: A mechanism based short review on common teratogenic agents Asian Pac J Trop Dis 2014; 4(6): 421-432 ASB2014-9573	N	LIT
KIIA 5.10 (OECD)	Jany, K.-D.	2013	Die Langzeitfütterungsstudie von Seralini et al. (2012) - eine kritische Replik Ernährungs Umschau 8/2013 ASB2014-9580	N	LIT
KIIA 5.10 (OECD)	Jasper, R.; Locatelli, G. O.; Pilati, C. et al.	2012	Evaluation of biochemical, hematological and oxidative parameters in mice exposed to the herbicide Glyphosate-Roundup Interdiscip Toxicol. 2012; Vol. 5(3): 133–140. ASB2014-9583	N	LIT
KIIA 5.10 (OECD)	Jayasumana, C.; Gunatilake, S.; Senanayake, P.;	2014	Glyphosate, hard water and nephrotoxic metals: Are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka? *Int. J. Environ. Res. Public Health* **2014**, *11*, 2125-2147 ASB2014-3085	N	LIT
KIIA 5.10 (OECD)	John, B.	2014	Letter to the editor Food and Chemical Toxicology:65 (2014) 391 ASB2014-9584	N	LIT
KIIA 5.10 (OECD)	Kachuri, L.; Demers, P. A.; Blair, A. et al.	2013	Multiple pesticide exposures and the risk of multiple myeloma in Canadian men Int. J. Cancer: 133, 1846–1858 (2013) ASB2014-8030	N	LIT
KIIA 5.10 (OECD)	Kamel, F.; Umbach, D. M.; Bedlack, R. S. et al.	2012	Pesticide exposure and amyotrophic lateral sclerosis NeuroToxicology 33 (2012) 457–462 ASB2014-9586	N	LIT

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KIIA 5.10 (OECD)	Kelce, W.R., Lamb, J.C., DeSesso, J.M.	2010	A Critique of prepubertal exposur eto commercial formulation of the herbicide glyphosate GLP: N, published: Y 2309848 / ASB2012-11867	N	LIT
KIIA 5.10 (OECD)	Kier, L. D.; Kirkland, D. J.	2013	Review of genotoxicity studies of Glyphosate and Glyphosate-based formulations Crit Rev Toxicol, 2013; 43(4): 283–315 ASB2014-9587	N	LIT
KIIA 5.10 (OECD)	Kilinc, N.; Isgör, M. M.; Sengül, B. et al.	2013	Influence of pesticide exposure on carbonic anhydrase II from sheep stomach Toxicology and Industrial Health 1–8 ASB2014-9588	N	LIT
KIIA 5.10 (OECD)	Kim, J.; Ko, W.; Lee, W. J.	2013	Depressive symptoms and severity of acute occupational pesticide poisoning among male farmers Occup Environ Med 2013;0:1–7 ASB2014-9592	N	LIT
KIIA 5.10 (OECD)	Kim, Y.; Hong, J.; Gil, H. et al.	2013	Mixtures of Glyphosate and surfactant TN20 accelerate cell death via mitochondrial damage-induced apoptosis and necrosis Toxicology in Vitro 27 (2013) 191–197 ASB2014-9591	N	LIT
KIIA 5.10 (OECD)	Kitazawa, T.		IET historical control data on milignant lymphoma incidence in control ICR (Crj:CD-1) mice HR-001: Carcinogenicity study in mice (IET 94-0151) 13-C015 ASB2014-9146		
KIIA 5.10 (OECD)	Knezevic, V.; Bozic, D.; Budosan, I. et al.	2012	Early continuous dialysis in acute Glyphosate-surfactant poisoning Srp Arh Celok Lek. 2012 Sep-Oct;140(9-10):648-652 ASB2014-9593	N	LIT
KIIA 5.10 (OECD)	Koller, V. J.; Fürhacker, M.; Nersesyan, A. et al.	2012	Cytotoxic and DNA-damaging properties of Glyphosate and Roundup in human-derived buccal epithelial cells Arch Toxicol (2012) 86:805–813 ASB2014-7618	N	LIT
KIIA 5.10 (OECD)	Koureas, M.; Tsezou, A.; Tsakalof, A. et al.	2014	Increased levels of oxidxative DNA damage in pesticide sprayers in Thessaly Region (Greece). Implications of pesticide exposure Science of the Total Environment 496 (2014) 358–364 ASB2014-9724	N	LIT

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KIIA 5.10 (OECD)	Koutros, S.; Andreotti, G.; Berndt, S. I. et al.	2011	Xenobiotic-metabolizing gene variants, pesticide use, and the risk of prostate cancer Pharmacogenetics and Genomics 2011, Vol 21 No 10 ASB2014-9594	N	LIT
KIIA 5.10 (OECD)	Krüger, M.; Schrödl, W.; Neuhaus, J.; Shehata, A. A.;	2013	Field investigations of glyphosate in urine of Danish dairy cows J Environ Anal Toxicol, 3:5 ASB2013-11599	N	---
KIIA 5.10 (OECD)	Krüger, M.; Shehata, A. A.; Schrödl, W.; Rodloff, A.;	2013	Glyphosate suppresses the antagonistic effect of *Enterococcus* spp. on *Clostridium botulinum* in Press, Anaerobe 20: 74-78 (2013) ASB2013-8527	N	---
KIIA 5.10 (OECD)	Krüger, M.; Schledorn, P.; Schrödl, W.; Hoppe, H. W.; Lutz, W.; Shehata, A. A.;	2014	Detection of Glyphosate residues in animals and humans J Environ Anal Toxicol 2014, 4:2 ASB2014-5024	N	LIT
KIIA 5.10 (OECD)	Krüger, M.;Große-Herrenthey, A.; Schrödl, W.; Gerlach, A.; Rodloff, A.;	2012	Visceral botulism at dairy farms in Schleswig Holstein, Germany - Prevalence of *Clostridium botulinum* in feces of cows, in animal feeds, in feces of the farmers, and in house dust Anaerobe 18 (2012) 221-223 ASB2013-13312	N	---
KIIA 5.10 (OECD)	Krüger, M.; Schrödl, W.; Pedersen, I; Shehata, A. A.	2014	Detection of Glyphosate in malformed piglets J Environ Anal Toxicol 2014, 4:5 ASB2014-8935	N	LIT
KIIA 5.10 (OECD)	Kumar, S.	2011	Occupational, environmental and lifestyle factors associated with spontaneous abortion Reproductive Sciences 18(10) 915-930 ASB2014-9725	N	LIT
KIIA 5.10 (OECD)	Kwiatkowska, M.; Huras, B.; Bukowska, B.	2014	The effect of metabolites and impurities of Glyphosate on human erythrocytes (in vitro) Pesticide Biochemistry and Physiology 109 (2014) 34–43 ASB2014-9603	N	LIT
KIIA 5.10 (OECD)	Kwiatkowska, M.; Nowacka-Krukowska, H.; Bukowska, B.	2014	The effect of Glyphosate, its metabolites and impurities on erythrocyte acetylcholinesterase activity Environ. Toxicol. Pharmacol. 37 (2014) 1101–1108 ASB2014-8085	N	LIT

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KIIA 5.10 (OECD)	Labite, H.; Cummins, E.	2012	A quantitative approach for ranking human health risks from pesticides in Irish groundwater Human and Ecological Risk Assessment, 18: 1156–1185, 2012 ASB2014-9604	N	LIT
KIIA 5.10 (OECD)	Lamb, J. C.; Bofetta, P.; Foster, W. G. et al.	2014	Critical comments on the WHO-UNEP state of the science of endocrine disrupting chemicals – 2012 Regulatory Toxicology and Pharmacology 69 (2014) 22–40 ASB2014-9605	N	LIT
KIIA 5.10 (OECD)	Larsen, K.; Najle, R.; Lifschitz, A.; Virkel, G.	2012	Effects of sub-lethal exposure of rats to the herbicide Glyphosate in drinking water: Glutathione transferase enzyme activities, levels of reduced Glutathione and lipid peroxidation in liver, kidneys and small intestine Environ. Toxicol. Pharmacol. 34(2012)811-818 ASB2014-6905	N	LIT
KIIA 5.10 (OECD)	Larsen, K.; Najle, R.; Lifschitz, A. et al.	2014	Effects of sublethal exposure to a Glyphosate-based herbicide formulation on metabolic activities of different xenobiotic-metabolizing enzymes in rats International Journal of Toxicology 2014, Vol. 33(4) 307-318 ASB2014-9606	N	LIT
KIIA 5.10 (OECD)	Lee, B. K.; Lee, H. K.; Ryu, H. H. et al.	2012	Continuous renal replacement therapy in a patient with cardiac arrest after Glyphosate-surfactant herbicide poisoning Hong Kong Journal of Emergency Medicine ASB2014-9607	N	LIT
KIIA 5.10 (OECD)	LeFew, W. R.; McConnell, E. R.; Crooks, J. L. et al.	2013	Evaluation of microelectrode array data using Bayesian modeling as an approach to screening and prioritization for neurotoxicity testing NeuroToxicology 36 (2013) 34–41 ASB2014-9608	N	LIT
KIIA 5.10 (OECD)	Lesmes-Fabian, C.; García-Santos, G.; Leuenberger, F. et al.	2012	Dermal exposure assessment of pesticide use: The case of sprayers in potato farms in the Colombian highlands Science of the Total Environment 430 (2012) 202–208 ASB2014-9726	N	LIT

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KIIA 5.10 (OECD)	Levine, S.	2012	EDSP assays and regulatory safety studies provide a weight of evidence that Glyphosate is not an endocrine disruptor SETAC North America 33rd Annual Meeting ASB2014-9609	N	LIT
KIIA 5.10 (OECD)	Lopez, S. L.; Aiassa, D.; Benitez-Leite, S.; Lajmanovich, R.; Manas, F.; Poletta, G.; Sanchez, N.; Simoniello, M. F.; Carrasco, A. E.;	2012	Pesticides used in South American GMO-based agriculture: A review of their effects on humans and animal models Advances in Molecular Toxicology, Volume 6, 41-75 doi.org/10.1016/B978-0-444-59389-4.00002-1 ASB2013-10534	N	---
KIIA 5.10 (OECD)	Malhotra, R.C., Ghia, D.K., Cordato, D.J., Beran, R.G.	2010	Glyphosate-surfactant herbicide-induced reversible encephalopathy Case Reports / Journal of Clinical Neuroscience 17 (2010) 1472–1473 ASB2012-11890	N	LIT
KIIA 5.10 (OECD)	Manas, F., Peralta, L., Raviolo, J., Ovando, H.G., Weyers, A., Ugnia, L., Cid, M.G., Larripa, I., Gorla, N.	2009	Genotoxicity of AMPA, the environmental metabolite of glyphosate, assessed by the Comet assay and cytogenetic tests Ecotoxicology and Environmental Safety 72, 834-837 GLP: N, published: Y 2309906 / ASB2012-11891	N	LIT
KIIA 5.10 (OECD)	Mandel, J.S., Alexander, B.H., Baker, B.A., Acquavella, J.F., Chapman, P., Honeycutt, R.	2005	Biomonitoring for farm families in the farm family exposure study Scand J Work Environ Health 31, 98-104 GLP: N, published: Y 2309910 / ASB2012-11893	N	LIT
KIIA 5.10 (OECD)	Mañas, F.; Peralta, L.; Ugnia, L. et al.	2013	Oxidative stress and comet assay in tissues of mice administered Glyphosate and Ampa in drinking water for 14 days Journal of Basic & Applied Genetics | 2013 | Volume 24 | Issue 2 | Article 7 ASB2014-6909		
KIIA 5.10 (OECD)	Manfo, F. P. T.; Moundipa, P. F.; Déchaud, H. et al.	2010	Effect of agropesticides use on male reproductive function: A study on farmers in Djutitsa (Cameroon) Environmental Toxicology ASB2014-9611		

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KIIA 5.10 (OECD)	Markard, C.;	2014	Umweltprobenbank des Bundes. Ergebnisse der Vorstudie "HBM von Glyphosat" II 1.2-93404/21 ASB2014-2057		
KIIA 5.10 (OECD)	Marc, J.; Mulner-Lorillon, O.; Boulben, S. et al.	2002	Pesticide Roundup provokes cell division dysfunction at the level of CDK1/Cyclin B activation Chemical Research in Toxicology 15:326-331 (2002) ASB2013-9838 / ASB2009-9012	N	---
KIIA 5.10 (OECD)	Marc, J., Belle, R., Morales, J., Cormier, P., Mulner-Lorillon, O.	2004	Formulated glyphosate activates the DNA-response checkpoint of the cell cycle leading to the prevention of G2/M transition Toxicological Sciences 82, 436-442 GLP: N, published: Y 2309912 / ASB2012-11894	N	LIT
KIIA 5.10 (OECD)	Marc, J., Mulner-Lorillon, O., Belle, R.	2004	Glyphosate-based pesticides affect cell cycle regulation Biology of the Cell 96, 245-249 GLP: N, published: Y 2309914 / ASB2009-9014	N	LIT
KIIA 5.10 (OECD)	Marc, J., Mulner-Lorillon, O., Durand, G., Belle, R.	2003	Embryonic cell cycle for risk assessment of pesticides at the molecular level Environmental Chemistry Letters 1, 8-12 GLP: N, published: Y 2309916 / ASB2009-9013	N	LIT
KIIA 5.10 (OECD)	Mariager, T. P.; Madsen, P. V.; Ebbehoj, N. E. et al.	2013	Severe adverse effects related to dermal exposure to a Glyphosate-surfactant herbicide Clinical Toxicology (2013), 51, 111–113 ASB2014-9612		
KIIA 5.10 (OECD)	Martini, C. M.; Gabrielli, M.	2012	A commercial formulation of Glyphosate inhibits proliferation and differentiation to adipocytes and induces apoptosis in 3T3-L1 fibroblasts Toxicology in Vitro 26 (2012) 1007–1013 ASB2014-9613		
KIIA 5.10 (OECD)	McConnell, E. R.; McClain, M. A.; Ross, J. et al.	2012	Evaluation of multi-well microelectrode arrays for neurotoxicity screening using a chemical training set NeuroToxicology 33 (2012) 1048–1057 ASB2014-9615		

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KIIA 5.10 (OECD)	McQueen, H., Callan, A.C., Hinwood, A.L.	2012	Estimating maternal and prenatal exposure to glyphosate in the community setting. International Journal of Hygiene and Environmental Health GLP: N, published: Y 2309926 / ASB2012-11898	N	LIT
KIIA 5.10 (OECD)	Mesnage, R., Clair, E., Gress, S., Then, C., Székács, A., Séralini, G.E.	2012	Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidal toxins alone or with a glyphosate-based herbicide Journal of Applied Toxicology:n/a-n/a GLP: N, published: Y 2309930 / ASB2012-11900	N	LIT
KIIA 5.10 (OECD)	Mesnage, R.; Moesch, C.; Le Grand, R. et al.	2012	Glyphosate exposure in a farmer's family Journal of Environmental Protection, 2012, 3, 1001-1003 ASB2014-3846		
KIIA 5.10 (OECD)	Mesnage R.; Defarge N.; Spiroux de Vendômois et al.	2014	Major pesticides are more toxic to human cells than their declared active principles Hindawi Publishing Corporation, BioMed Reserch International Vol 2014 ASB2014-1755		
KIIA 5.10 (OECD)	Mesnage, R.; Séralini, G.-E.	2014	The need for a closer look at pesticide toxicity during GMO assessment Practical Food Safety: Contemporary Issues and Future Directions, First Edition. Edited by Rajeev Bhat and Vicente M. Gómez-López. ASB2014-9616		
KIIA 5.10 (OECD)	Mink, P. J.; Mandel, J. S.; Sceurman, B. K. et al.	2012	Epidemiologic studies of Gyphosate and cancer: A review Regulatory Toxicology and Pharmacology 63 (2012) 440–452 ASB2014-9617		
KIIA 5.10 (OECD)	Modesto, K. A.; Martinez, C. B. R.	2010	Effects of roundup transorb on fish: Hematology, antioxidant defenses and acetylcholinesterase activity Chemosphere 81 (2010) 781–787 ASB2012-811		
KIIA 5.10 (OECD)	Moreno, N. C.; Sofia, S. H.; Martinez, C. B. R.;	2014	Genotoxic effects of the herbicide RoundupTransorb®and its active ingredient glyphosate onthe fish Prochilodus lineatus Environ. Toxicol. Pharmacol. 37 (2014) 448–454 ASB2014-7522		

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KIIA 5.10 (OECD)	Mose, T., Kjaerstad, M.B., Mathiesen, L., Nielsen, J.B., Edelfors, Sn., Knudsen L.E.	2008	Placental passage of benzoic acid, caffeine, and glyphosate in an ex vivo human perfusion system Journal of Toxicology and Environmental Health-Part a-Current Issues 71, 984-991 GLP: N, published: Y 2309958 / ASB2012-11914	N	LIT
KIIA 5.10 (OECD)	Mostafalou, S.; Abdollahi, M.	2013	Pesticides and human chronic diseases: Evidences, mechanisms, and perspectives Toxicology and Applied Pharmacology 268 (2013) 157–177 ASB2014-9618		
KIIA 5.10 (OECD)	Mulet, J.M.	2011	Letter to the Editor Regarding the Article by Paganelli et al. Chemical Research in Toxicology 24, 609 GLP: N, published: Y 2309962 / ASB2012-11916	N	MOD
KIIA 5.10 (OECD)	NABU	2011	Glyphosat & Ag rogentechnik - Risiken des Anbaus herbizidresistenter Pflanzen für Mensch und Umwelt Ausgabe: 04/2011 ASB2012-8016		
KIIA 5.10 (OECD)	Narayan, S.; Liew, Z.; Paul, K. et al.	2013	Household organophosphorus pesticide use and Parkinson's disease International Journal of Epidemiology 2013;1–10 ASB2014-9620		
KIIA 5.10 (OECD)	Niemann, L.; Sieke, C.; Pfeil, R.; Solecki, R.;	2014	A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers *in Press J. Verbr. Lebensm., (2015) 10:3-12* ASB2014-11029		
KIIA 5.10 (OECD)	Omran, N. E.; Salama, W. M.;	2013	The endocrine disrupter effect of atrazine and glyphosate on Biomphalaria alexandrina snails Toxicology and Industrial Health 1–10 ASB2014-7614		
KIIA 5.10 (OECD)	Paumgartten, F.J.R. Cremonese, C. Freiere, C. Meyer, A. Koiman, S.	2012	Pesticide exposure and poor pregnancy outcomes: weaknesses of the evidence // Exposição a agrotóxicos e resultados adversos da gravidez: a fragilidade da evidência Cad. Saúde Pública, Rio de Janeiro, 28(10):2009-2012, out, 2012 ASB2013-10538	N	---

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KIIA 5.10 (OECD)	Paganelli, A., Gnazzo, V., Acosta, H., Lopez, S.L., Carrasco, A.E.	2010	Glyphosate-Based Herbicides Produce Teratogenic Effects on Vertebrates by Impairing Retinoic Acid Signaling Chem Res Toxicol 23, 1586-1595 GLP: N, published: Y 2309994 / ASB2012-11986, ASB2010-11410	N	LIT
KIIA 5.10 (OECD)	Pahwa, P. P.; Karunanayak, C. P.; Dosman, J. A. et al.	2011	Soft-tissue sarcoma and pesticides exposure in men results of a canadian case-control study JOEM _ Volume 53, Number 11, November 2011 ASB2014-9625		
KIIA 5.10 (OECD)	Palma, G.	2011	Letter to the Editor Regarding the Article by Paganelli et al. Chemical Research in Toxicology 24, 775-776 GLP: N, published: Y 2310000 / ASB2012-11989	N	LIT
KIIA 5.10 (OECD)	PANAP	2009	Glyphosate - Summary ASB2012-8017		
KIIA 5.10 (OECD)	Perry, L.; Adams, R. D.; Benett, A. R. et al.	2014	National toxicovigilance for pesticide exposures resulting in health care contact – An example from the UK's National poisons information service Clinical Toxicology (2014), 52, 549–555 ASB2014-9626		
KIIA 5.10 (OECD)	Quassinti, L., Maccari, E., Murri, O., Bramucci, M.	2009	Effects of paraquat and glyphosate on steroidogenesis in gonads of the frog Rana esculenta *in vitro* Pesticide Biochemistry and Physiology 93, 91-95 GLP: N, published: Y 2310038 / ASB2012-12007	N	MOD
KIIA 5.10 (OECD)	Razi, M.; Najaft, G.; Feyzi, S. et al.	2012	Histological and histochemical effects of Glyphosate on testicular tissue and function Iran J Reprod Med Vol. 10. No. 3. pp: 181-192, May 2012 ASB2014-9390		
KIIA 5.10 (OECD)	Relyea, A.R.	2005	The impact of insecticides and herbicides on the biodiversity and productivity of aquatic communities Ecological Applications, 15(2), 2005, pp. 618–627 ASB2012-204		

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KIIA 5.10 (OECD)	Relyea, A.R.	2012	New effects of Roundup on amphibians: Predators reduce herbicide mortality; herbicides induce antipredator morphology Ecological Applications, 22(2), 2012, pp. 634–647 ASB2012-2791		
KIIA 5.10 (OECD)	Rhomberg, L. R.; Goodman, J. E.	2012	Low-dose effects and nonmonotonic dose–responses of endocrine disrupting chemicals: Has the case been made? Regulatory Toxicology and Pharmacology 64 (2012) 130–133 ASB2014-9391		
KIIA 5.10 (OECD)	Richard, S., Moslemi, S., Sipahutar, H., Benachour, N., Seralini, G.E.	2005	Differential effects of glyphosate and roundup on human placental cells and aromatase Environmental Health Perspectives 113, 716-720 GLP: N, published: Y 2310042 / ASB2009-9024 / TOX2005-1743	N	LIT
KIIA 5.10 (OECD)	Riede, S.; Schafft, H.; Lahrssen-Wiederholt, M.; Breves, G.;	2014	Effects of a glyphosate-based herbicide on in vitro ruminal fermentation and microbial community with special attention to clostridia. Proc. Soc. Nutr. Physiol. ; VOL 23 2014; 23; 34 Gesellschaft fur Ernahrungsphysiologie Conference; 68th, Gesellschaft fur Ernahrungsphysiologie ASB2013-14684		
KIIA 5.10 (OECD)	Roberts, J. R.; Karr, C. J.	2012	Pesticide exposure in children PEDIATRICS Volume 130, Number 6, December 2012 ASB2014-9394		
KIIA 5.10 (OECD)	Rodloff, A. C.; Krüger, M.;	2012	Chronic *Clostridium botulinum* infections in farmers Anaerobe 18 (2012) 226-228 ASB2013-13311	N	---
KIIA 5.10 (OECD)	Romano, M., Romano, R., Santos, L., Wisniewski, P., Campos, D., de Souza, P., Viau, P., Bernardi, M., Nunes, M., de Oliveira, C.	2012	Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression Archives of Toxicology 86, 663-673 GLP: N, published: Y 2310048 / ASB2012-12011	N	LIT

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KIIA 5.10 (OECD)	Romano, R.M., Romano, M.A., Bernardi, M.M., Furtado, P.V., Oliveira, C.A.	2010	Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology Arch Toxicol 84, 309317 GLP: N, published: Y 2310050 / ASB2012-12012	N	LIT
KIIA 5.10 (OECD)	Romano, M. A.; Romano, R. M.	2012	Reply to comment of John M. DeSesso and Amy L. Williams regarding "Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression" by Romano et al. 2012 Arch Toxicol (2012) 86:1795–1797 ASB2014-9396		
KIIA 5.10 (OECD)	Rosanoff, A.	2014	Letter to the editor Food and Chemical Toxicology: 65 (2014) 389 ASB2014-9397		
KIIA 5.10 (OECD)	Roberfroid, M.	2014	Letter to the editor Food and Chemical Toxicology: 65 (2014) 390 ASB2014-9393		
KIIA 5.10 (OECD)	Roberfroid, M.	2014	Letter to the editor Food and Chemical Toxicology: 66 (2014) 385 ASB2014-9392		
KIIA 5.10 (OECD)	Roustan, A.; Aye, M.; De Meo, M.; Di Giorgio, C.;	2014	Genotoxicity of mixtures of glyphosate and atrazine and their environmental transformation products before and after photoactivation Chemosphere 108 (2014) 93–100 ASB2014-8086		
KIIA 5.10 (OECD)	Rowe, L. D.; Lovering, S. L.; Martin, B. W.; Harvey, R. B.; Peterson, H. D.; Farr, F. M.; Moore, E. G.; Long, T. J.	1987	The subacute oral toxicity of the isopropylamine salt of glyphosate (MON 0139) in female cattle 82002 ! VT-82-003 TOX9552424	N	---
KIIA 5.10 (OECD)	Rowe, L. D.; Lovering, S. L.; Martin, B. W.; Harvey, R. B.; Peterson, H. D.; Farr, F. M.; Moore, E. G.; Long, T. J.	1987	The subacute toxicity of Roundup herbicide (MON-2139) in female cattle 82001 ! VT-82-002 ASB2010-8131	N	---

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KIIA 5.10 (OECD)	Rowe, L. D.; Lovering, S. L.; Martin, B. W.; Wilson, R. D.; Peterson, H. D.; Farr, F. M.; Moore, E. G.	1987	The acute toxicity of glyphosate in female goats 80006 ! VT-80-450 TOX9552422	N	---
KIIA 5.10 (OECD)	Rowe, L. D.; Lovering, S. L.; Martin, B. W.; Wilson, R. D.; Peterson, H. D.; Farr, F. M.; Moore, E. G.	1987	The acute oral toxicity of the isopropylamine salt of glyphosate (MON 0139) in female goats 80007 ! VT-80-451 TOX9552423	N	---
KIIA 5.10 (OECD)	Saltmiras, D., Bus, J.S., Spanogle, T., Hauswirth, J., Tobia, A., Hill, S.	2011	Letter to the Editor Regarding the Article by Paganelli et al. Chemical Research in Toxicology 24, 607-608 GLP: N, published: Y 2310056 / ASB2012-12015	N	LIT
KIIA 5.10 (OECD)	Saltmiras, D.A., Tobia, A.	2012	No Evlidence of Endocrine Disruption by Glyphosate in Hershberger and Uterotrophic Assays. Abstract PS 2198 The Toxicologist (supplement to Toxicological Sciences) 126, 474 GLP: N, published: Y 2310058 / ASB2012-12016	N	LIT
KIIA 5.10 (OECD)	Samsel, A.; Seneff, S.	2013	Glyphosate's suppression of Cytochrome P450 enzymes and amino acid biosynthesis by the Gut Microbiome: Pathways to modern diseases Entropy 2013, 15, 1416-1463 ASB2013-8535		
KIIA 5.10 (OECD)	Savitz, D.A., Arbuckle, T., Kaczor, D., Curtis, K.M.	1997	Male pesticide exposure and pregnancy outcome American Journal of Epidemiology 146, 1025-1036 GLP: N, published: Y 2310070 / ASB2012-12022	N	LIT
KIIA 5.10 (OECD)	Schinasi, L.; Leon, M. E.;	2014	Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: A systematic review and meta-analysis Int. J. Environ. Res. Public Health 2014, 11, 4449-4527 ASB2014-4819		

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KIIA 5.10 (OECD)	Seneff, S.; Lauritzen, A.; Davidson, R. M. et al.	2013	Is encephalopathy a mechanism to renew sulfate in autism? Entropy 2013, 15, 372-406 ASB2014-9729		
KIIA 5.10 (OECD)	Sengupta, P.; Banerjee, R.	2013	Environmental toxins: Alarming impacts of pesticides on male fertility Human and Experimental Toxicology 1-23 ASB2014-9730		
KIIA 5.10 (OECD)	Séralini, G. E.	2014	Conclusiveness of toxicity data and double standards Food and Chemical Toxicology 69 (2014) 357–359 ASB2014-9632		
KIIA 5.10 (OECD)	Seyboldt, C.; Hoedemaker, M.;	2014	Bedeutung von Clostridium botulinum bei chronischem Krankheitsgeschehen und Teilprojekt: Mikrobiologisches Risikopotenzial von Biogasanlagen unter besonderer Berücksichtigung von Hühnertrockenkot als Gärsubstrat. Abschlussbericht Projekt: 2810HS005 Tierärztliche Hochschule Hannover ASB2014-10736		
KIIA 5.10 (OECD)	Shehata, A. A.; Schrödl, W.; Aldin, A. A.; Hafez, H. M.; Krüger, M.;	2012	The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro Curr Microbiol, published online 09.12.2012 ASB2012-16301	N	---
KIIA 5.10 (OECD)	Shehata, A.; Schrödl, W.; Neuhaus, J.; Krüger, M.;	2012	Antagonistic effect of different bacteria on *Clostridium botulinum* types A, B, D and E *in vitro* Downloaded from veterinaryrecord.bmj.com on December 19, 2012 ASB2013-8529	N	---
KIIA 5.10 (OECD)	Sirinathsinghji, E.;	2014	Sri Lanka Partially Bans Glyphosate for Deadly Kidney Disease Epidemic ISIS Report 09/04/14 ASB2014-10742		
KIIA 5.10 (OECD)	Sørensen, M. T.; Damgaard Poulsen, H.; Højberg, O.	2014	Memorandum on "The feeding of genetically modified Glyphosate resistant soy products to livestock" ASB2014-5761		

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BVL registration number	Data protection claimed Y/N	Owner[5]
KIIA 5.10 (OECD)	Song, H. Y.; Kim, J. H.; Seok, S. J.; Gil, H. W.; Hong, S, Y.;	2012	*In vitro* cytotoxic effect of glyphosate mixture containing surfactants J Korean Med Sci 2012; 27: 711-715 ASB2013-10531	N	---
KIIA 5.10 (OECD)	Sribanditmong-kol, P.; Jutavijit-tum, P.; Pon-graveevongsa, P.; Wunnapuk, K.; Durongka-dech, P.	2012	Pathological and toxicological findings in Glyphosate-surfactant herbicide fatality Am J Forensic Med Pathol & Volume 33, Number 3, September 2012 ASB2014-9731		
KIIA 5.10 (OECD)	Sugeng, A. J.; Beamer, P. I.; Lutz, E. A. et al.	2013	Hazard-ranking of agricultural pesticides for chronic health effects in Yuma County, Arizo-na Science of the Total Environment 463-464 (2013) 35–41 ASB2014-9733		
KIIA 5.10 (OECD)	Takahashi, H.; Kakinuma, Y.	1992	Ammonium salt of glyphosate (MON 8750) general pharmacology study IET 90-0149/ET-92-15 TOX9552421	N	---
KIIA 5.10 (OECD)	Thongprakai-sang, S.; Thi-antanawat, A.; Rangkadilok, N.; Suriyo, T.; Satayavivad, J.;	2013	Glyphosate induces human breast cancer cells growth via estrogen receptors Food and Chemical Toxicology, 59(2013)129–136 ASB2013-11991	N	---
KIIA 5.10 (OECD)	Tizhe, E. V.; Ibrahim, N. D. G.; Fatihu, M. Y. et al.	2013	Haematogical changes induced by subchronic Glyphosate exposure: Ameliorative effect of zinc in Wistar rats Sokoto Journal of Veterinary Sciences, Vol-ume 11 (Number 2). December, 2013 ASB2014-6963		
KIIA 5.10 (OECD)	Tizhe, E. V.; Ibrahim, N. D. G.; Fatihu, M. Y. et al.	2013	Influence of zinc supplementation on histo-pathological changes in the stomach, liver, kidney, brain, pancreas and spleen during sub-chronic exposure of Wistar rats to Glyphosate Comp Clin Pathol (2013) ASB2014-6965		
KIIA 5.10 (OECD)	Tizhe, E. V.; Ibrahim, N. D. G.; Fatihu, M. Y. et al.	2013	Serum biochemical assessment of hepatic and renal functions of rats during oral exposure to Glyphosate with zinc Comp Clin Pathol (2014) 23:1043–1050 ASB2014-6964		

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KIIA 5.10 (OECD)	Vandenberg, L. N.; Colborn, T.; Hayer, T. B. et al.	2012	Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses Endocrine Reviews, June 2012, 33(3):378–455 ASB2014-9635		
KIIA 5.10 (OECD)	Walsh, L.P., McCormick, C., Martin, C., Stocco, D.M.	2000	Roundup inhibits steroidogenesis by disrupting steroidogenic acute regulatory (StAR) protein expression Environmental Health Perspectives 108, 769-776 GLP: N, published: Y 2310118 / ASB2012-12046	N	LIT
KIIA 5.10 (OECD)	Wigle, D. T.; Arbuckle, T. E.; Turner, M. C.; Bérube, A.; Yang, Q.; Liu, S.; Krewski, D.	2008	Epidemiologic evidence of relationships be-tween reproductive and child health outcomes and environmental chemical contaminants Journal of Toxicology and Environmental Health, Part B, 11:373–517, 2008 ASB2014-9637		
KIIA 5.10 (OECD)	Williams, A.L., Watson, R.E., DeSesso, J.M.	2012	Developmental and Reproductive Outcomes in Humans and Animals After Glyphosate Exposure: A Critical Analysis Journal of Toxicology and Environmental Health, Part B 15, 39-96 GLP: N, published: Y 2310130 / ASB2012-12052	N	LIT
KIIA 5.10 (OECD)	Wood, E.	1996	Glyphosate Technical: Pharmacology Screening Study in the Rat 434/021 NUF GLP: Y, published: N 2310134 / ASB2012-12054	Y	NUF
KIIA 5.10 (OECD)	Wunnapuk, K.; Gobe, G.; Endre Z. et al.	2013	Use of a glyphosate-based herbicide-induced nephrotoxicity model toinvestigate a panel of kidney injury biomarkers Toxicology Letters 225 (2014) 192– 200 ASB2014-9638		
KIIA 5.10 (OECD)	Xia, S.; Zhao, Y.-B.; Yang, M.-Q. et al.	2013	Induction of vitellogenin gene expression in medaka exposed to Glyphosate and potential molecular mechanism China Environmental Science 2013, 33(9): 1656-1663 ASB2014-9642		

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KIIA 5.10 (OECD)	Yang, W.; Carmichael, S. L.; Roberts, E. M. et al.	2013	Residential agricultural pesticide exposures and risk of neural tube defects and orofacial clefts among offspring in the San Joaquin Valley of California American Journal of Epidemiology ASB2014-9644		
KIIA 5.10 (OECD)	Yousef, M.I., Salem, M.H., Ibrahim, H.Z., Helmi, S., Seehy, M.A., Bertheussen, K.	1995	Toxic effects of carbofuran and glyphosate on semen characteristics in rabbits Journal of Environmental Science and Health Part B-Pesticides Food Contaminants and Agricultural Wastes 30, 513-534 GLP: N, published: Y 2310142 / ASB2012-12058	N	LIT
KIIA 5.10 (OECD)	Zhang, Z.-L.; Yang, Z.-F.	2013	Research Progress on Rep roductive and Developmental Toxicity of Glyphosate J Environ o.:.:up Med. reb.2013 Vol.30 "",,.2 ASB2014-9643		
KIIA 5.10 (OECD)	Zhao, W.; Yu, H.; Zhang, J. et al.	2013	Effects of Glyphosate on apoptosis and expressions of androgen-binding protein and vimentin mRNA in mouse Sertoli cells J South Med Univ, 2013, 33(11): 1709-1712 ASB2014-9645		
KIIA 5.10 (OECD)	Zouaoui, K.; Dulaurent, S.; Gaulier, J. M. et al.	2012	Determination of Glyphosate and AMPA in blood and urine from humans: About 13 cases of acute intoxication Forensic Science International (2012) ASB2014-9734		
KIIIA1 7.1.1 (OECD)	Blaszcak, D.L. & Auletta, C.S	1991	Acute Oral Toxicity Study In Rats BD-91-261 MON GLP: Y, published: N 2315976 / TOX9552438	N	MOD
KIIIA1 7.1.2 (OECD)	Blaszcak, D.L. & Auletta, C.S	1991	Acute Dermal Toxicity Study In Rats BD-91-262 MON GLP: Y, published: N 2315978 / TOX9552439	N	MOD
KIIIA1 7.1.3 (OECD)	Polveche, V . Rombaut, M. Bonicelli, B.	1999	Measurements of granulometry and distribution of a spray nozzle - Comparison of different glyphosate formulations 106/Pulv MON GLP: N, published: N 2315980 / ASB2012-12069	N	MOD
KIIIA1 7.1.3 (OECD)	Velasquez, D. J.	1982	Acute inhalation toxicity of Roundup formulation to male and female Sprague-Dawley rats - incl. Amendment No. 1, Date: 15.12.1982 810093 ! ML-81-201 TOX2002-693	N	---

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KIIIA1 7.1.4 (OECD)	Blaszcak, D.L. Auletta, C.S	1991	Primary dermal irritation study in rabbits BD-91-263 MON GLP: Y, published: N 2315983 / TOX9552440	N	MOD
KIIIA1 7.1.5 (OECD)	Blaszcak, D.L. Auletta, C.S	1991	Primary eye irritation study in rabbits BD-91-60 MON GLP: Y, published: N 2315985 / TOX9552441	N	MOD
KIIIA1 7.1.6 (OECD)	Blaszcak, D. L.; Levitz, E. C.;	1987	Genamin T-200 BM: A closed-patch repeated insult dermal sensitization study in guinea pigs - (Buehler method) 6816-86 ! BD-86-290 ASB2010-366	N	---
KIIIA1 7.1.6 (OECD)	Griffon, B.	2001	Skin sensitization test in guinea pigs (Modified Buehler test: 9 applications) CI-2001-153 MON GLP: Y, published: N 2315987 / TOX2005-1135	N	MOD
KIIIA1 7.4 (OECD)	Martin, S.; Westphal, D.; Erdtmann-Vourliotis, M.; Dechet, F.; Schulze-Rosario, C.; Stauber, F.; Wicke, H.; Chester, G.	2008	Guidance for exposure and risk evaluation for bystanders and residents exposed to plant protection products during and after application 2008/1070089 ! 1661-5751/00/000001-10 ! DOI 10.1007/s00003-008-0361-5 ASB2009-450	N	---
KIIIA1 7.5 (OECD)	Krebs. B.; Maasfeld, W.; Schrader, J.; Wolf, R.; Hoernicke, E.; Nolting, H. G.; Backhaus, G. F.; Westphal, D.	2000	Uniform Principles for safeguarding the health of workers re-entering crop-growing areas after application of plant protection product TOX2004-1971	N	---
KIIIA1 7.6.2 (OECD)	Davies, D.J.	2003	Glyphosate SL (360 g/L) Formulation (A12798Q): in vitro absorption through human epidermis CTL JV1732 SYN GLP: Y, published: N 2309514 / ASB2012-11518	Y	SYN

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KIIIA1 7.6.2 (OECD)	Hadfield, N.	2011	Glyphosate 360 IPA Salt (CA2273): *In Vitro* Absorption through Human Epidermis using [^{14}C]-glyphosate JV2147-REG NUF GLP: Y, published: N 2309512 / ASB2012-11517	Y	NUF
KIIIA1 7.6.2 (OECD)	EFSA	2012	Panel on Plant Protection Products and their Residues (PPR). Guidance on Dermal Absorp-tion. EFSA Journal (2012), 10(4), 2665-2695, ASB2012-6959	N	---
KIIIA1 7.6.2 (OECD)	Franz, T.J.	1983	Evaluation of the percutaneous absorption of Roundup formulations in man using an *in-vitro* technique MON GLP: N, published: N 2309488 / TOX9552417	N	MON
KIIIA1 7.6.2 (OECD)	OECD	2011	Guidance notes on dermal absorption. Adopted 18 August 2011. Series on Testing and As-sessment, No. 156. ENV/JM/MONO(2011)36, JT03305971. ASB2013-2 http://www.oecd.org/dataoecd/63/12/48532204.pdf.	N	---
KIIIA1 7.6.2 (OECD)	Ward, R.J.	2010	360 g/L Glyphosate SL Formulation (MON 52276) - *In vitro* absorption of glyphosate through human epidermis JV2084-REG MON GLP: Y, published: N 2315989 / ASB2012-5383	Y	MOD
KIIIA1 7.6.2 (OECD)	Ward	2010	450 g/L Glyphosate SL Formulation (MON 79545) - *In vitro* absorption of glyphosate through human epidermis JV2083-REG MON GLP: Y, published: N 2309508 / ASB2012-11515	Y	MON
KIIIA1 7.6.2 (OECD)	Ward	2010	480 g/L Glyphosate SL Formulation (MON 79351) - *In vitro* absorption of glyphosate through human epidermis JV2085-REG MON GLP: Y, published: N 2309510 / ASB2012-11516	Y	MON
KIIIA1 7.6.2 (OECD)	Wester, R. C.; Melendres, J.; Sarason, R.; McMaster, J.; Maibach, H. I.	1991	Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination TOX9552418	N	---

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KIIIA1 7.6.2 (OECD)	Wester, R.C., Quan, D., Maibach, H.I., Wester, R.M.	2005	Percutaneous Absorption of Hazardous Chemicals from Fabric into and Through Human Skin. In Percutaneous Absorption: Drugs, Cosmetics, Mechanisms, Methods Boca Raton, FL. Taylor and Francis Group, LLC. 22, 303-310 GLP: N, published: Y 2310126 / ASB2012-12050	N	LIT
KIIIA1 7.6.3 (OECD)	EPA	2009	Alkyl Amine Polyalkoxylates; Exemption from the requirement of a tolerance Fed. Reg. 74(2009)115:28616 ASB2009-9022	N	---
KIIIA1 7.6.3 (OECD)	Fillmore, G. E.	1973	G-3780: 14-week oral subacute study in dogs 33372 ! MRD-165 ! XX-95-336 ! MON 0818 ASB2009-9026	N	---
KIIIA1 7.6.3 (OECD)	Hahn, A.; Be-gemann, K.; Burger, R. Hillebrand, J, Meyer, H. Preußner, K. Gessener, M	2007	Ärztliche Mitteilungen bei Vergiftungen 2007, BfR ASB2013-4034	N	---
KIIIA1 7.6.3 (OECD)	Holson, J.F.	1989	A dose range-finding developmental toxicity study of MON 0818 in rats. WIL Research Labs., Ashland, Ohio, USA, on behalf of Monsanto. Project no. WIL-50042, Sponsor no. WI-88-304, unpublished; ASB2009-9028	N	---
KIIIA1 7.6.3 (OECD)	Holson, J. F.	1990	A develomental toxicity study of MON 0818 in rats, Final report: WI-89-388 GLP: N, published: Y 2309808 / ASB2009-9029	N	LIT
KIIIA1 7.6.3 (OECD)	Jauhiainen, A.; Räsänen, K.; Sarantila, R.; Nuutinen, J.; Kangas, J.	1991	Occupational exposure of forest workers to glyphosate during brush saw spraying work American Industrial Hygiene Association Journal, 52(1991)2:61-64 MET9600092	N	---
KIIIA1 7.6.3 (OECD)	Knapp, J.F.	2007	A ReproductionDevelopmental Toxicity Screening Study of MON 0818 in Rats WIL-50282 GLP: Y, published: N 2309858 / ASB2010-365	Y	MOD

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KIIIA1 7.6.3 (OECD)	Knapp, J.F.	2008	A Combined 28-Day Repeated Dose Oral (Dietary) Toxicity Study with the Reproduction/DevelopmentalToxicity Screening Test of MON 8109 and MON 0818 in Rats WIL-50337 MON GLP: N, published: N 2309861 / ASB2010-364	N	MOD
KIIIA1 7.6.3 (OECD)	Martinez, T. T.; Long, W. C.; Hiller, R.	1990	Comparison of the toxicology of the herbicide Roundup by oral and pulmonary routes of exposure Z44833	N	---
KIIIA1 7.6.3 (OECD)	Stella, J., Ryan, M.	2004	Glyphosate herbicide formulation: a potentially lethal ingestion Emerg Med Australas 16, 235-239 GLP: N, published: Y 2310102 / ASB2012-12038	N	LIT
KIIIA1 7.6.3 (OECD)	Stout, L. D	1990	Ninety-day study of MON 0818 administered in feed to albino rats MSL-10468 ! ML-89-359/EHL 89161 ASB2009-9027	N	---
KIIIA1 7.6.3 (OECD)	Tai, T.; Yamashita, M.; Wakimori, H.	1990	Hemodynamic effects of Roundup, glyphosate and surfactant in dogs The Japanese Journal of Toxicology, 3, 63-68. TOX9552419	N	---
KIIIA1 7.6.3 (OECD)	Zoetis, T	1991	Subchronic toxicity study in rats with Atmer 163. Hazleton Washington, Inc., Vienna, Virginia, USA, on behalf of ICI Americas, submitted by Monsanto. HWA 564-162 ASB2009-10488	N	---
KIIIA1 7.9 (OECD)	BfR; Hahn, A.; Begemann, K.; Burger, R. et al.	2007	Ärztliche Mitteilungen bei Vergiftungen ISBN 3-938163-40-2 ! ISSN 1435-4047 ASB2014-9290		

Codes of owner

ALK	Alkaloida Europe
ALS	Alschu-Chemie GmbH
CHE	Cheminova A/S
EGT	European Glyphosate Task Force AIR 2
EXC	ExxonMobile Chemical Belgium
ADM	ADAMA Agan Ltd
HAG	Handelsgesellschaft für Baustoffe mbH & Co. KG
HEL	Helm AG
JCC	Jiangsu Changlong

LIT	Published literature
MAH	Makhteshim-AGAN Group
MOD	Monsanto Europe S.A./N.V.
MON	Montedison (Deutschland) Chemie Handels GmbH
NUF	Nufarm GmbH & Co. KG
SYN	Syntana Handelsgesellschaft

To: Nguyen, Khue[Nguyen.Khue@epa.gov]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]; HEERING, DAVID C [AG/1000][david.c.heering@monsanto.com]; HEYDENS, WILLIAM F [AG/1000][william.f.heydens@monsanto.com]; NYANGULU, JAMES M [AG/1920][james.m.nyangulu@monsanto.com]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Lowit, Anna[Lowit.Anna@epa.gov]; Perron, Monique[Perron.Monique@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Bloem, Thomas[Bloem.Thomas@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Thur 4/7/2016 9:40:15 PM
Subject: RE: notes from April 5 glyphosate meeting

Hello Khue:

Thank you for your email, we'll get back to you shortly.

Best Regards,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Wednesday, April 06, 2016 2:57 PM
To: JENKINS, DANIEL J [AG/1920]; LISTELLO, JENNIFER J [AG/1000]; HEERING, DAVID C [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; NYANGULU, JAMES M [AG/1920]
Cc: Anderson, Neil; Moriarty, Thomas; Smith, Charles; Lowit, Anna; Perron, Monique; Dunbar, Anwar; Bloem, Thomas
Subject: notes from April 5 glyphosate meeting

Hi all,

Thanks for attending the meeting on glyphosate yesterday. We thought it was a very productive discussion. Attached, please find the notes from the meeting and the sign-in sheet for your records. Please feel free to send edits/corrections for the notes if you feel that EPA has mischaracterized anything.

The notes outline the information that HED requested during the meeting yesterday. As you know, this information request is time sensitive—**would it be possible for Monsanto to send the bibliography that was discussed by April 15th?**

Also, as a side note, in the email to Monsanto dated 3/31/16, the list of epi studies gives the impression that there were 12 studies cited, but we double checked and it was a copy/paste error and there are only 6 epi studies.

Thanks again for being so responsive to our request for information.

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

To: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]; david.c.heering@monsanto.com[david.c.heering@monsanto.com]; william.f.heydens@monsanto.com[william.f.heydens@monsanto.com]; NYANGULU, JAMES M [AG/1920][james.m.nyangulu@monsanto.com]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Lowit, Anna[Lowit.Anna@epa.gov]; Perron, Monique[Perron.Monique@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Bloem, Thomas[Bloem.Thomas@epa.gov]
From: Nguyen, Khue
Sent: Wed 4/6/2016 6:57:22 PM
Subject: notes from April 5 glyphosate meeting
glyphosate monsanto meeting notes after team comments 4.6.16.docx
sign in sheet for monsanto meeting on 4.5.16.pdf

Hi all,

Thanks for attending the meeting on glyphosate yesterday. We thought it was a very productive discussion. Attached, please find the notes from the meeting and the sign-in sheet for your records. Please feel free to send edits/corrections for the notes if you feel that EPA has mischaracterized anything.

The notes outline the information that HED requested during the meeting yesterday. As you know, this information request is time sensitive—**would it be possible for Monsanto to send the bibliography that was discussed by April 15th?**

Also, as a side note, in the email to Monsanto dated 3/31/16, the list of epi studies gives the impression that there were 12 studies cited, but we double checked and it was a copy/paste error and there are only 6 epi studies.

Thanks again for being so responsive to our request for information.

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

Glyphosate: 4/5/16 meeting between EPA and Monsanto—notes

EPA met with Monsanto to discuss EPA's recent information request for glyphosate. In an email dated 3/21/16, EPA requested information on the inert ingredients used in popular US and European formulations of glyphosate in the present day and also dating back to the 80s. EPA was particularly interested in information on how glyphosate formulations have changed over time in the last 20-30 years. In its email request, EPA included a list of 6 epi studies that were completed in the mid-1980s to the early 2000s; these studies were cited in the IARC's recent report on glyphosate. EPA included this list of studies because it was interested in characterizing potential differences in US and European glyphosate epidemiology studies.

Monsanto briefly discussed the epi studies that were referenced in EPA's 3/21/16 email and discussed why they may not give an accurate picture of glyphosate's carcinogenicity. Monsanto also briefly discussed glyphosate's history of safety and the conclusions of various regulatory agencies all over the world, many of which conclude that glyphosate was not carcinogenic.

EPA stated that at this time it was not interested in discussing the opinions of other regulatory agencies nor was it interested in debating glyphosate's carcinogenicity at the April 5 meeting. Rather, EPA stated that it was in the midst of a large scale holistic review of the glyphosate database. EPA's approach for registration review risk assessment is to take a systematic and scientific, weight of the evidence approach, and would not rely on the regulatory conclusions of other regulatory agencies. In an effort to resolve questions about the potential toxicity of glyphosate, glyphosate formulations, and any co-formulants (inert ingredients and surfactants), EPA was interested in any data or information Monsanto may have on how the formulations may differ from data on the active ingredient and surfactants independently of one another.

Of particular interest to EPA are the following:

1) Toxicity (particularly repeat dose data) or pharmacokinetic formulation studies.
2) Information on the pharmacokinetics of glyphosate, including info on tissue dosimetry or metabolism.
3) *In vitro* studies on bioactivity (including cellular-based bioactivity).
4) Any *in vitro* ADME (absorption, distribution, metabolism, and excretion) studies
5) Any remaining carcinogenicity studies on glyphosate not yet submitted to EPA. At some point in the future, the agency may be interested in other toxicities (*e.g.*, developmental or reproductive toxicity).

EPA requested that rather than sending to the agency all the studies that might be relevant, Monsanto should start with a bibliography that EPA can use to compare with its own bibliography. The agency requested that Monsanto include data generated for both North American registrations as well as European registrations. Then EPA would be able to indicate which of these studies would be of potential use in its analysis and make a request for them. EPA indicated that this should be done as soon as possible.

There was also some discussion about changes in Monsanto's Roundup formulation over the years. Monsanto indicated that up until 2000, nearly all glyphosate products on the market were its Roundup formulation which used some form of tallow amine as a surfactant. Afterwards, the properties of

surfactants used and the ratio of surfactant to active ingredient were changed in most formulations due to a need for increased ai loading. Current products vary geographically due to various reasons, some having to do with marketing. EPA suggested that Monsanto provide in writing any information that documents the changes of glyphosate formulations over time and across the globe.

The agency appreciates Monsanto's cooperation in its attempt to conduct a thorough and transparent science-driven analysis of the human health effects of glyphosate under registration review.

Name	Org	email
David Heering	MON	david.c.heering@monsanto.com
Jennifer Listello	MON	jjlist@monsanto.com
Bill Heydens	MON	william.f.heydens@monsanto.com
James Nyangulu	MON	james.m.nyangulu@monsanto.com
Dan Jenkins	MON	daniel.j.jenkins@monsanto.com
Anwar Dunbar	HED	dunbar.anwar@epa.gov
Monique Perron	HED	perron.monique@epa.gov
Tom Bloem	HED	bloem.thomas@epa.gov
NEIL ANDERSON	EPA/PRD	ANDERSON.NEIL@EPA.GOV
Reuben Baris	EPA/RD	baris.reuben@epa.gov
[illegible]	[illegible]	[illegible]
Charles Smith	EPA/HED	smith.charles@epa.gov
Anna Lowit	EPA/HED	lowit.anna@epa.gov
Cecilia Tan	EPA/HED	tan.cecilia@epa.gov
Khue Nguyen	EPA/PRD	nguyen.khue@epa.gov

Glyphosate: 4/5/16 meeting with Monsanto—notes

EPA met with Monsanto to discuss EPA's recent information request for glyphosate. In an email dated 3/21/16, EPA requested information on the inert ingredients used in popular US and European formulations of glyphosate in the present day and also dating back to the 80s. EPA was particularly interested in information on how glyphosate formulations have changed over time in the last 20-30 years. In its email request, EPA included a list of 6 epi studies that were completed in the mid-1980s to the early 2000s; these studies were cited in the IARC's recent report on glyphosate. EPA included this list of studies because it was interested in characterizing potential differences in US and European glyphosate epidemiology studies.

Monsanto briefly discussed the epi studies that were referenced in EPA's 3/21/16 email and discussed why they may not give an accurate picture of glyphosate's carcinogenicity. Monsanto also briefly discussed glyphosate's history of safety and the conclusions of various regulatory agencies all over the world, many of which conclude that glyphosate was not carcinogenic.

EPA stated that it was not interested in discussing the opinions of other regulatory agencies in the world nor was it interested in debating glyphosate's carcinogenicity or lack of carcinogenicity. Rather, EPA was in the midst of a large scale holistic review of the glyphosate database. EPA's approach for registration review risk assessment is a scientific, weight of the evidence approach, and would not depend on the regulatory conclusions of other regulatory agencies. In an effort to resolve questions about glyphosate's synergism with inert ingredients and surfactants, EPA was more interested in any information Monsanto may have on its formulations and how data on the formulations may differ from data on the active ingredient.

Of particular interest to EPA are the following:

1) Formulation studies that might be tox-related, dermal-related, or related to pharmacokinetics.
2) Information on the pharmacokinetics of glyphosate, including info on tissue dosimetry or metabolism.
3) Information on the tox profile of common formulations.
4) In vitro studies on bioactivity (including cellular-based bioactivity).
5) Any in vitro ADME (absorption, distribution, metabolism, and excretion) studies

EPA suggested that rather than sending to the Agency all the studies that might be relevant, Monsanto should start with a bibliography that EPA can use to compare with its own bibliography. Then EPA would be able to ID studies that were not in its database and make a request for them. EPA indicated that this should be done as soon as possible. [Do we want to give Monsanto a deadline? Maybe by April 15th?]

There was some discussion about changes in Monsanto's Roundup formulations over the years. Monsanto indicated that up until 2000, pretty much all glyphosate formulations on the market were its Roundup formulation. Afterwards, the surfactants used and the ratio of surfactant to active ingredient may have been changed due to a need for increased ai loading. Current products vary geographically due to various reasons, some having to do with marketing.

Nguyen, Khue

From: Nguyen, Khue
Sent: Thursday, March 31, 2016 5:28 PM
To: 'JENKINS, DANIEL J [AG/1920]'
Cc: Smith, Charles; Anderson, Neil; Moriarty, Thomas
Subject: meeting next week

Hi Dan,

I'm forwarding additional details from our human health folks about the meeting next week:

As part of Registration Review, the agency has been evaluating the extensive data that is available for glyphosate, including the IARC and EFSA reports on carcinogenicity. This has included a toxicological analysis consisting of a wide variety of experimental animal data and *in vitro* data from the guideline studies and from the scientific literature. In addition we are evaluating the epidemiological database of about a dozen US and European studies. In order to better characterize the significant toxicological and epidemiological data that is available for glyphosate in the registration review preliminary risk assessment, the agency has been attempting to determine changes over the last 20 or 30 years in the use of glyphosate products over time (i.e., which formulations have dominated the market). EPA is also interested in how the inert compounds used in the major glyphosate products utilized in agricultural settings in the US and in Europe have changed over the last 20 or 30 years. The agency is particularly interested in utilizing this data to help characterize any potential differences in the US and European glyphosate epidemiology studies (mid 1980s – early 2000s, see list below). We would like to discuss this in more detail during next week's meeting.

List of glyphosate epidemiology studies:

De Roos, A. J., Blai r, A., Rusiecki, J. A., Hoppin, J. A., Svec, M., Dosemeci, M., Alavanja, M. C. (2005) . Cancer incidence among glyphosate-exposed
pesticide applicators in the Agricultural Health Study. *Environ Health Perspect, 113(1),* 49- 54.

De Roos, A. J., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Holmes, F. F., Burmeister, L. F., & Blair, A. (2003). Integrative assessment of multiple
pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med,* 60(9), Ell.

Eriksson, M., Hardell, L., Carlberg, M., & Akerman, M. (2008). Pesticide exposure as risk factor for non-Hodgkin lymphoma including
histopathological subgroup analysis. *Int J Cancer, 123(7),* 1657-1663.

Hardell, L., Eriksson, M., & Nordstrom, M. (2002) . Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled
analysis of two Swedish case-control studies. *Leuk Lymphoma,* 43(5), 1043- 1049.

McDuffie, H. H., Pahwa, P., Mclaughlin, J. R., Spinelli, J. J., Fincham, S., Dosman, J. A., Choi, N. W. (2001) . Non-Hodgkin's lymphoma and specific
pesticide exposu res in men: cross -Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev,* 10(11), 1155-1163.

Orsi, L., Delabre, L., Monnereau, A., Delval, P., Berthou, C., Fenaux, P., Clave!, J. (2009). Occupational exposure to pesticides and lymphoid
neoplasms among men: results of a French case-control study. *Occupational and Environmental Medicine,* 66(5), 291-298.

111 De Roos, A. J., Blai r, A., Rusiecki, J. A., Hoppin, J. A., Svec, M., Dosemeci, M., Alavanja, M. C. (2005). Cancer incidence among glyphosate-exposed
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Orsi, L., Delabre, L., Monnereau, A., Delval, P., Berthou, C., Fenaux, P., Clave!, J. (2009) . Occupational exposure to pesticides and lymphoid
neoplasms among men: results of a French case-control study. *Occupational and Environmental Medicine,* 66(5), 291-298.

Let me know if you have any questions.

Thanks,

Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
703-347-0248
Nguyen.khue@epa.gov

To: Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]; Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; HEYDENS, WILLIAM F [AG/1000][william.f.heydens@monsanto.com]; NYANGULU, JAMES M [AG/1920][james.m.nyangulu@monsanto.com]
From: JENKINS, DANIEL J [AG/1920]
Sent: Fri 3/25/2016 4:11:32 PM
Subject: Re: glyphosate call next week

Hi Khue:

We'll take Tuesday 4/5 3-4 pm

Thanks,

Dan Jenkins
US Agency Lead
Monsanto Company
202 383 2851 (o)
571 732 6575 (c)

On Mar 24, 2016, at 1:59 PM, Nguyen, Khue <Nguyen.Khue@epa.gov> wrote:

Hi Dan,

I'm sorry to do this to you, but we just found out that April 5th 11:30 will not work for us because of an all-hands meeting for all divisions (we just got notice today). Let's try this again with alternate proposed times:

Monday 4/4, 1-2pm

Tuesday 4/5, 3-4 pm

Wedn 4/6, 1-2 pm, also

If none of these times work, we will have to schedule something during the lunch hr on one of the days (although EPA staff don't really like that). You are busy next week. I am on vacation for 2.5 weeks starting on 4/8. So we have to schedule this the week of 4/4.

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Thursday, March 24, 2016 2:42 PM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>
Cc: Anderson, Neil <Anderson.Neil@epa.gov>; Moriarty, Thomas <Moriarty.Thomas@epa.gov>; Smith, Charles <Smith.Charles@epa.gov>
Subject: Re: glyphosate call next week

Hi Khue:

11:30-12:30 ET on Tues April 5th works for us.

Dan Jenkins

US Agency Lead

Monsanto Company

202.383.2851 office

571.732.6575 cell

On Mar 23, 2016, at 4:06 PM, Nguyen, Khue <Nguyen.Khue@epa.gov> wrote:

Hi Dan,

I hope you are well. I was wondering if you had some time next week for a call about glyphosate. We are seeking some historical information on the inert ingredients used in certain glyphosate products that belong to Monsanto. Here are some proposed times for a call:

Tues 3-4 pm (March 29^{th})

Wedn 3-4 pm (March 30^{th})

Thurs 1-2 pm (March 31^{st})

Let us know.

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

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To: Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]
From: JENKINS, DANIEL J [AG/1920]
Sent: Thur 3/24/2016 6:42:44 PM
Subject: Re: glyphosate call next week

Sorry meant to copy Jen Listello

Dan Jenkins
US Agency Lead
Monsanto Company
202.383.2851 office
571.732.6575 cell

On Mar 24, 2016, at 1:42 PM, JENKINS, DANIEL J [AG/1920] <daniel.j.jenkins@monsanto.com> wrote:

> Hi Khue:
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Thurs 1-2 pm (March 31st)

Let us know.

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

To: Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Thur 3/24/2016 6:42:08 PM
Subject: Re: glyphosate call next week

Hi Khue:

11:30-12:30 ET on Tues April 5th works for us.

Dan Jenkins
US Agency Lead
Monsanto Company
202.383.2851 office
571.732.6575 cell

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Let us know.

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

To: Anderson, Neil[Anderson.Neil@epa.gov]; Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: Moriarty, Thomas[Moriarty.Thomas@epa.gov]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]
From: JENKINS, DANIEL J [AG/1920]
Sent: Wed 2/17/2016 2:40:30 PM
Subject: RE: glyphosate slides from meeting in early June

Hey Neil:

Again, just wanted to make EPA aware of some additional publically available info- another relevant publication came out last week from the German Regulators (BfR)

http://www.bfr.bund.de/en/press_information/2016/08/bfr_study_confirms__no_glyphosate_detectable_in_breas
196578.html

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Anderson, Neil [mailto:Anderson.Neil@epa.gov]
Sent: Tuesday, January 26, 2016 9:44 PM
To: JENKINS, DANIEL J [AG/1920]; Nguyen, Khue
Cc: Moriarty, Thomas; LISTELLO, JENNIFER J [AG/1000]
Subject: Re: glyphosate slides from meeting in early June

Thank you Dan for forwarding this to us. We also recently saw a publication by Jensen, et al about another method for detecting glyphosate and AMPA in breast milk. We will make certain the right people here are made aware of this recent pub.

Regards,

Neil

From: JENKINS, DANIEL J [AG/1920] <daniel.j.jenkins@monsanto.com>
Sent: Tuesday, January 26, 2016 8:38 PM
To: Nguyen, Khue
Cc: Moriarty, Thomas; Anderson, Neil; LISTELLO, JENNIFER J [AG/1000]
Subject: Re: glyphosate slides from meeting in early June

Hi All:

Wanted to make you aware of this publication re glyphosate and breast milk

http://pubs.acs.org/doi/abs/10.1021/acs.jafc.5b05852

Dan Jenkins

US Agency Lead

Monsanto Company

202.383.2851 office

571.732.6575 cell

On Oct 27, 2015, at 9:22 AM, Nguyen, Khue <Nguyen.Khue@epa.gov> wrote:

> Hi Dan,

Yes, that is fine. Please send to my attention at this address:

Pesticide Reevaluation Division

One Potomac Yard

2777 S. Crystal Drive

Arlington, VA 22202

Thank you!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, October 27, 2015 10:11 AM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>
Cc: Moriarty, Thomas <Moriarty.Thomas@epa.gov>; Anderson, Neil <Anderson.Neil@epa.gov>
Subject: RE: glyphosate slides from meeting in early June

Hi:

One of the slides is CBI so we don't want to email. Can we submit to the 4th floor on a CD to your attention?

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Monday, October 19, 2015 10:59 AM
To: JENKINS, DANIEL J [AG/1920]
Cc: Moriarty, Thomas; Anderson, Neil
Subject: glyphosate slides from meeting in early June

Good morning Dan,

I hope you are well!

Do you recall the meeting that we had with Monsanto back in early June on glyphosate? I have been searching through my emails and electronic files for the PowerPoint that was presented by Monsanto, but was unable to find it. Can you please forward to us a copy of the PowerPoint presentation from the meeting on June 4th?

Please be sure to note slides containing CBI or where you wish information to be redacted, in case we post the presentation in the public docket for glyphosate.

Thanks!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

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To: Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Anderson, Neil[Anderson.Neil@epa.gov]; LISTELLO, JENNIFER J [AG/1000][jennifer.j.listello@monsanto.com]
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Sent: Wed 1/27/2016 1:38:12 AM
Subject: Re: glyphosate slides from meeting in early June

Hi All:

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http://pubs.acs.org/doi/abs/10.1021/acs.jafc.5b05852

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Thank you!

Khue Nguyen

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703-347-0248

Nguyen.khue@epa.gov

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MONSANTO

MONSANTO COMPANY
1300 I (EYE) STREET, NW
SUITE 450E
WASHINGTON, D.C. 20005-7211
PHONE: (202) 783-2460
FAX: (202) 789-1867
http://www.monsanto.com

September 8, 2015

Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA

RE: EPA Reg. No. 71995-25 (Roundup® Weed & Grass Killer Super Concentrate)

Hi Khue,

This letter is in response to your recent e-mail query dated September 3, 2015 about the lb ae/gal information for one of our products with EPA Reg. No.71995-25 (L&G Roundup Weed & Grass Killer Super Concentrate). The Roundup® Weed & Grass Killer Super Concentrate product contains 3.7 lb / gallon ae glyphosate.

Please let me know if you need anything else from us.

Sincerely,

James M. Nyangulu, PhD
U.S. Agency Regulatory Affairs Manager

CC: Daniel Jenkins
Jennifer Listello

Glyphosate Registration Review Meeting with Monsanto
Monday, March 30, 2015
2:30 pm – 3:00 pm

Name	Affiliation	Email
Carissa Cyran	EPA/PRD	Cyran.carissa@epa.gov
Amy Blankinship	EPA/EFED	blankinship.amy@epa.gov
James Hetrick	EPA/EFED	hetrick.james@epa.gov
Rosanna Louie-Juzwiak	EPA/EFED	louie-juzwiak.rosanna@epa.gov
Tom Moriarty	EPA/OPP	moriarty.thomas@epa.gov
Colwell Cook	EPA/BEAD	cook.colwell@epa.gov
Dana Spatz	EPA/EFED	spatz.dana@epa.gov
Eric Sachs	Monsanto	eric.s.sachs@monsanto.com
Dan Jenkins	MONSANTO	djjenk@MONSANTO.com
Jennifer Listello	Monsanto	jjlist@monsanto.com
Chad E. Wujcik	MONSANTO	chad.e.wujcik@monsanto.com
Rick Keigwin	EPA/PRD	Keigwin.richard@epa.gov

Glyphosate Human Health Risk Assessment Meeting with Monsanto
Monday, March 30, 2015
3:00 pm – 4:00 pm

Name	Affiliation	Email
Carissa Cyran	EPA/PRD	Cyran.carissa@epa.gov
Rick Keigwin	EPA/PRD	keigwin.richard@epa.gov
Charles Smith	EPA/HED	smith.charles@epa.gov
Monique Perron	EPA/HED	perron.monique@epa.gov
Tom Moriarty	EPA/PRD	moriarty.thomas@epa.gov
Julie Van Alstine	EPA/HED	vanalstine.julie@epa.gov
David Miller	EPA/HED	miller.davidj@epa.gov
Jennifer Listello	MON	jjlist@monsanto.com
Dan Jenkins	MON	djjenk@monsanto.com
Eric Sachs	MON	eric.s.sachs@monsanto.com
Yu-Ting Guilaran	EPA/BEAD	Guilaran.Yu-Ting@epa.gov
Wynne Miller	EPA/BEAD	miller.wynne@epa.gov
Attendees who participated via conference call:		
Derek Berwald	EPA/BEAD	
Thuy Nguyen	EPA/BEAD	
Marian Bleeke	MON	
Pam Jensen	MON	

SIGN IN SHEET—Glyphosate: meeting with Monsanto—6/4/15

Name	Organization	Email
Khue Nguyen	PRD/EPA	Nguyen.khue@epa.gov
MICHAEL HORAK	MONSANTO	MJHORA@MONSANTO.COM
JAMES NYANGULU	MONSANTO	james.m.nyangulu@monsanto.com
CHAD WUJCIK	MONSANTO	chad.e.wujcik@monsanto.com
ERIC SACHS	MONSANTO	ERIC.S.SACHS@MONSANTO.COM
Jennifer Listello	Monsanto	jjlist@monsanto.com
Rosanna Louie-Juzwiak	EPA/EFED	louie-juzwiak.rosanna@epa.gov
Dana Spatz	EPA/EFED	spatz.dana@epa.gov
Thurston Morton	EPA/HED	morton.thurston@epa.gov
Monique Perron	EPA/HED	perron.monique@epa.gov
Tom Bloem	EPA/HED	bloem.thomas@epa.gov
NEIL ANDERSON	EPA/PRD	ANDERSON.NEIL@EPA.GOV
DAN JENKINS	MONSANTO	djjenk@monsanto.com
Tom Moriarty	EPA/OPP	moriarty.thomas@epa.gov
Caitlin Newcamp	EPA/PRD	
THUY NGUYEN	EPA/BEAD	
STEVE LEVINE		
STEVE ADAMS		
PAM JENSEN		
LEAH RITER	MONSANTO	
MARIAN BLEEKE	VIA PHONE	
DAVID SALTMIRAS		

To: Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Anderson, Neil[Anderson.Neil@epa.gov]; PRIVOTT, NATALIE R [AG/1920][natalie.r.privott@monsanto.com]
From: JENKINS, DANIEL J [AG/1920]
Sent: Tue 10/27/2015 2:23:35 PM
Subject: RE: glyphosate slides from meeting in early June

Nat:

Please have the CD couriered over to Khue Nguyen's attn per below.

Thanks,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Tuesday, October 27, 2015 10:22 AM
To: JENKINS, DANIEL J [AG/1920]
Cc: Moriarty, Thomas; Anderson, Neil
Subject: RE: glyphosate slides from meeting in early June

Hi Dan,

Yes, that is fine. Please send to my attention at this address:

Pesticide Reevaluation Division

One Potomac Yard

2777 S. Crystal Drive

Arlington, VA 22202

Thank you!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, October 27, 2015 10:11 AM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>
Cc: Moriarty, Thomas <Moriarty.Thomas@epa.gov>; Anderson, Neil <Anderson.Neil@epa.gov>
Subject: RE: glyphosate slides from meeting in early June

Hi:

One of the slides is CBI so we don't want to email. Can we submit to the 4th floor on a CD to your attention?

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Monday, October 19, 2015 10:59 AM
To: JENKINS, DANIEL J [AG/1920]
Cc: Moriarty, Thomas; Anderson, Neil
Subject: glyphosate slides from meeting in early June

Good morning Dan,

I hope you are well!

Do you recall the meeting that we had with Monsanto back in early June on glyphosate? I have been searching through my emails and electronic files for the PowerPoint that was presented by Monsanto, but was unable to find it. Can you please forward to us a copy of the PowerPoint presentation from the meeting on June 4th?

Please be sure to note slides containing CBI or where you wish information to be redacted, in case we post the presentation in the public docket for glyphosate.

Thanks!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

To: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]
Cc: Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Anderson, Neil[Anderson.Neil@epa.gov]
From: Nguyen, Khue
Sent: Tue 10/27/2015 2:21:44 PM
Subject: RE: glyphosate slides from meeting in early June

Hi Dan,

Yes, that is fine. Please send to my attention at this address:

Pesticide Reevaluation Division

One Potomac Yard

2777 S. Crystal Drive

Arlington, VA 22202

Thank you!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, October 27, 2015 10:11 AM

To: Nguyen, Khue <Nguyen.Khue@epa.gov>
Cc: Moriarty, Thomas <Moriarty.Thomas@epa.gov>; Anderson, Neil <Anderson.Neil@epa.gov>
Subject: RE: glyphosate slides from meeting in early June

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Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Monday, October 19, 2015 10:59 AM
To: JENKINS, DANIEL J [AG/1920]
Cc: Moriarty, Thomas; Anderson, Neil
Subject: glyphosate slides from meeting in early June

Good morning Dan,

I hope you are well!

Do you recall the meeting that we had with Monsanto back in early June on glyphosate? I have been searching through my emails and electronic files for the PowerPoint that was presented by Monsanto, but was unable to find it. Can you please forward to us a copy of the PowerPoint presentation from the meeting on June 4th?

Please be sure to note slides containing CBI or where you wish information to be redacted, in case we post the presentation in the public docket for glyphosate.

Thanks!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

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To: Nguyen, Khue[Nguyen.Khue@epa.gov]
Cc: Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Anderson, Neil[Anderson.Neil@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Tue 10/27/2015 2:11:01 PM
Subject: RE: glyphosate slides from meeting in early June

Hi:

One of the slides is CBI so we don't want to email. Can we submit to the 4th floor on a CD to your attention?

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Monday, October 19, 2015 10:59 AM
To: JENKINS, DANIEL J [AG/1920]
Cc: Moriarty, Thomas; Anderson, Neil
Subject: glyphosate slides from meeting in early June

Good morning Dan,

I hope you are well!

Do you recall the meeting that we had with Monsanto back in early June on glyphosate? I have been searching through my emails and electronic files for the PowerPoint that was presented by Monsanto, but was unable to find it. Can you please forward to us a copy of the PowerPoint presentation from the meeting on June 4th?

Please be sure to note slides containing CBI or where you wish information to be redacted, in case we post the presentation in the public docket for glyphosate.

Thanks!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

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To: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]
Cc: Anderson, Neil[Anderson.Neil@epa.gov]; Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Blankinship, Amy[Blankinship.Amy@epa.gov]
From: Nguyen, Khue
Sent: Mon 7/27/2015 10:32:44 PM
Subject: RE: response to glyphosate questions

Hi Dan,

Please see our responses to the remaining questions for glyphosate below in red.

Is the Agency performing a "rate based" environmental assessment with crop and non-crop application scenarios in the PRA, similar to what was used for the Glyphosate California red-legged frog assessment (Pages 31-32; Table 2.6)?

EFED response: While not using the exact methodology as was used in the red-legged frog RA, EFED did evaluate application rates beyond lb a.e./A. EFED used the master use tables prepared by the task force when evaluating the lb a.e./A application rates.

Have the "newer" submitted Syngenta sponsored avian reproduction studies (NOEC =2250 ppm) and adult honey bee acute studies (NOEC =200 ug a.i./bee) been used as new measurement endpoints in the assessment?

EFED response: EFED did review and incorporate the additional avian reproduction and honeybee toxicity studies in the RA.

Let me know if you have additional questions.

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Thursday, July 23, 2015 2:05 PM
To: Nguyen, Khue
Cc: Anderson, Neil; Moriarty, Thomas
Subject: RE: response to glyphosate questions

Hi Khue:

Any update from EFED?

Also, this came out today: http://www.eurekalert.org/pub_releases/2015-07/wsu-wrf072315.php

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East

Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Nguyen, Khue [mailto:Nguyen.Khue@epa.gov]
Sent: Thursday, June 25, 2015 5:09 PM
To: JENKINS, DANIEL J [AG/1920]
Cc: Anderson, Neil; Moriarty, Thomas
Subject: response to glyphosate questions

Hi Dan,

Please see below for our responses in red.

Is the Agency performing a "rate based" environmental assessment with crop and non-crop application scenarios in the PRA, similar to what was used for the Glyphosate California red-legged frog assessment (Pages 31-32; Table 2.6)? We will get back to you on this, EFED has been sent this question.

When will the Tier 1 EDSP WoE document be available for Glyphosate and can the overall conclusion be shared from the WoE document? Soon, within several weeks.

We heard at Rick Keigwin's recent meeting with CLA that the Agency will be issuing DCIs for honey bee testing for actives currently going through reg review. Considering existing information and the PRA, will Glyphosate receive a DCI for additional bee testing and if so which study(s) would be required? It is likely that we will require additional pollinator data for glyphosate. We intend to do the same for all chemicals with outdoor uses with potential exposure to honeybees, but we have not determined when or which studies yet.

Have the "newer" submitted Syngenta sponsored avian reproduction studies (NOEC =2250 ppm) and adult honey bee acute studies (NOEC =200 ug a.i./bee) been used as new measurement endpoints in the assessment? We will get back to you on this, EFED has been sent this question.

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

To: Anderson, Neil[Anderson.Neil@epa.gov]
From: BNA Highlights
Sent: Wed 5/4/2016 8:25:07 PM
Subject: May 4 -- BNA, Inc. Daily Environment Report - Afternoon Briefing

Afternoon Briefing - Your Preview of Today's News

The following news provides a snapshot of what Bloomberg BNA is working on today. Read the full version of all the stories in the final issue, published each night.

Science Committee Seeks Answers on EPA Glyphosate Report

Posted May 04, 2016, 4:02 P.M. ET

By David Schultz

The chairman of the House Science Committee is seeking answers from the Environmental Protection Agency about its handling of a report on the cancer-causing potential of a widely used pesticide.

In a letter today to EPA Administrator Gina McCarthy, Rep. Lamar Smith (R-Texas) said the EPA's handling of a report from its Cancer Assessment Review Committee on the weed killer glyphosate "raises questions about the agency's motivations in providing a fair assessment of glyphosate" and "may shed light on larger systemic problems occurring at the agency."

The EPA report found that glyphosate, the signature pesticide developed by Monsanto, likely does not cause cancer. The finding contradicted a recent World Health Organization finding.

The agency posted the report online April 29, apparently inadvertently. The report was taken down three days later, after Bloomberg BNA reported on it. Smith asked McCarthy to turn over all internal communications relating to the report to his committee.

Garland Could Boost Environmental Rules If Confirmed: CRS

Posted May 04, 2016, 2:34 P.M. ET

By Anthony Adragna

Confirming Judge Merrick Garland to the Supreme Court could result in "somewhat more favorable" odds for environmental regulations, the Congressional Research Service said in a report.

Garland, who was nominated by President Barack Obama to replace the late Justice Antonin Scalia on March 16, has typically been deferential to federal agencies' interpretations of their statutory responsibilities, based on dozens of environmental cases the judge has participated in during his 19 years on the U.S. Court of Appeals for the District of Columbia Circuit, researchers concluded.

“Where a number of observers have suggested that Justice Scalia evidenced a certain degree of skepticism toward arguments emphasizing environmental values, Judge Garland generally has been viewed as more receptive to such arguments, even though he has not always ruled in favor of environmental protections,” the report said.

“Overall, it appears that agencies defending environmental rules could find their odds somewhat more favorable in many cases if Judge Garland were to be confirmed,” it concluded.

Arizona Court Becomes Third to Dismiss Water Rule Lawsuit

Posted May 04, 2016, 2:25 P.M. ET

By Amena H. Saiyid

A federal district court in Arizona late yesterday became the third court to dismiss a lawsuit filed against the federal rule clarifying the scope of Clean Water Act over waters and wetlands.

The U.S. District Court for the District of Arizona dismissed the challenge after the U.S. Court of Appeals for the Sixth Circuit reaffirmed April 21 that it—rather than a district court—would serve as the proper venue to hear challenges against the Clean Water Rule (RIN 2040-AF30).

District courts in Arizona, Ohio and Oklahoma have now dismissed cases; 11 other lawsuits are pending against the Clean Water Rule in federal district courts. The Clean Water Rule was jointly promulgated by the Environmental Protection Agency and the U.S. Army Corps of Engineers last June.

Poll Details Climate Views of Trump, Clinton, Sanders Voters

Posted May 04, 2016, 12:18 P.M. ET

By Anthony Adragna

Over half of the supporters of remaining presidential candidates Donald Trump (R), Hillary Clinton (D) and Sen. Bernie Sanders (I-Vt.) believe climate change is real, though fewer than half of Trump's backers (45 percent) think it's primarily caused by human activity, according to polling released today.

The report by the Yale Program on Climate Change Communication and George Mason Center for Climate Change Communication found that most Trump's supporters favored funding additional research into renewable energies (76 percent), tax credits for energy-efficiency purchases (70 percent) and regulating carbon dioxide as a pollutant (62 percent). More than 90 percent of Clinton and Sanders supporters favored those same policies.

And 85 percent of Clinton backers, 88 percent of Sanders supporters, and 51 percent of Trump supporters said they were in favor of a requiring fossil fuel companies to pay a carbon tax.

Moniz: Carbon Price Needed for 2050 Climate Goal

Posted May 04, 2016, 1:25 P.M. ET

By Ari Natter

The U.S. will need to put a price on carbon to meet its 2050 climate goal of reducing carbon dioxide emissions by 80 percent, Energy Secretary Ernest Moniz said May 4.

“I think eventually we are going to need an economy-wide legislative approach,” Moniz said during remarks at a climate forum organized by the European Union. “Eventually some administration will be working with Congress on a more comprehensive legislative solution.”

A tax on carbon is among the possible policy options, Moniz said.

Though the Republican-controlled Congress, as well as oil companies and other large carbon emitters, have had little appetite for policy that would price carbon, the “continued drive to lower costs [in the energy sector] will enable much easier policymaking, Moniz said.

Wildlife Service Proposes Boosting Take Limit for Bald Eagles

Posted May 04, 2016, 4:10 P.M. ET

By Carolyn Whetzel

U.S. Fish and Wildlife Service officials today proposed boosting the annual incidental take limit for bald eagles from 1,103 to 4,200 nationwide, an increase they said reflects the continued growth in the eagle populations.

The take limit for golden eagles would remain at zero, unless those deaths or injuries are mitigated, under proposed changes to regulations designed to protect the two eagle species from unintentional harm from legal activities, like wind and renewable energy developments.

At the same time, the FWS released a proposed programmatic environmental impact statement to support the proposed "improvements" to regulations.

EPA Decades' Delay in Fracking Wastewater Rules Alleged

Posted May 04, 2016, 3:57 P.M. ET

By Andrew Harris

The U.S. Environmental Protection Agency was accused of being almost 30 years late in issuing rules for the handling of wastewater from oil and gas exploration, delaying to act even as frackers' disposal of it triggers earthquakes.

Environmental groups, including the Environmental Integrity Project and the Natural Resources Defense Council, filed a lawsuit today in the U.S. District Court of the District of Columbia seeking an order compelling the EPA to adopt measures regulating the disposal. They say the need for them has become more acute with the prevalence of fracking, the pumping of sand, water and chemicals into underground shale formations to free natural gas and oil from the rock.

Increased earthquake activity "in the vicinity of injection wells has been documented in Alabama, Arkansas, Colorado, Kansas, New Mexico, Ohio, Oklahoma and Texas," according to the groups' complaint.

They say the absence of disposal rules poses a threat to human and environmental health.

Melissa Harrison, a spokeswoman for the EPA, declined to comment immediately on the allegations.

Wastewater from fracking contains potentially harmful pollutants, including naturally occurring radioactive materials, that can be dangerous if they're released into the environment or if people are exposed to them, according to a 2012 Natural Resources Defense Council study. Frackers rid themselves of wastewater by injecting it into the underground wells.

U.S., Canada to 'Institutionalize' Regulatory Cooperation

Posted May 04, 2016, 1:55 P.M. ET

By Pat Rizzuto

The U.S. and Canada aim to make regulatory cooperation part of regulatory agencies' daily practice, senior officials said today.

"We have to institutionalize regulatory cooperation going forward," Howard Shelanski, administrator of the U.S. Office of Information and Regulatory Affairs, told regulators and industry representatives from both countries. They meet through tomorrow to discuss ongoing and new opportunities for the Canada-United States Regulatory Cooperation Council, or RCC.

The RCC's collaboration on the transport of hazardous materials, energy efficiency standards and new chemicals over the last five years has shown binational efforts can get goods to market more quickly while protecting safety, human health and the environment, Shelanski said.

New and modified RCC work plans will be released by June, said Iain Stewart, associate secretary of Canada's Treasury Board.

Net Benefits in Environmental Mitigation Weighed

Posted May 04, 2016, 3:13 P.M. ET

By Alan Kovski

Federal agencies can sometimes require companies to mitigate development with a net conservation benefit, going beyond a no-net-loss standard, but the authority to do so varies by law and agency, an Interior Department official said today.

Gary Frazer, assistant director for endangered species in the U.S. Fish and Wildlife Service, offered the example of his own agency as he spoke at an Environmental Law Institute event.

The FWS has latitude to negotiate habitat improvements when it grants a right-of-way across a national wildlife refuge, but it does not appear to have a similar authority when formulating a habitat conservation plan under the Endangered Species Act, Frazer said.

The subject was given an added impetus when President Barack Obama issued a presidential memorandum Nov. 3 telling federal agencies to aim for net benefits in environmental mitigation when the laws allow.

U.S. Officials Seek Survival of Regulatory Cooperation

Posted May 04, 2016, 12:20 P.M. ET

By Cheryl Bolen

Top officials at the Office of Information and Regulatory Affairs sought to reassure both U.S. and Canadian industry groups today that regulatory cooperation between the two trading nations would survive the upcoming transition in administrations.

Dominic Mancini, deputy administrator at OIRA and the top career employee at that agency who will oversee the transition to the next administration, said he strongly supports the ongoing regulatory cooperation efforts between the U.S. and Canada. "The executive orders that establish this as a priority don't expire with the current president, so I can say with confidence that we will emphasize . . . with the next administration the success of regulatory cooperation, in Canada in particular," he said.

In February 2011, President Barack Obama and then-Canadian Prime Minister Stephen Harper created the U.S.-Canada Regulatory Cooperation Council (RCC) to promote economic growth and job creation and to benefit consumers and businesses through increased regulatory transparency and coordination. The RCC is scheduled to finalize its latest work plans by early summer.

China: Hebei Province Lax in Environmental Protection

Posted May 04, 2016, 1:59 P.M. ET

By Michael Standaert

In a rare public rebuke of a regional government, China announced that the province of Hebei, which surrounds the polluted capital of Beijing, is failing to seriously adopt environmental protection efforts.

The Ministry of Environmental Protection called Hebei's actions to protect the environment "far away from the requirements of the central government and public expectations."

The province failed to adequately invest in air pollution abatement measures in recent years, permitted illegal projects in protected areas, and continued to build coal-fired power plants despite orders to cut coal consumption, the government said.

China's central government is continuing to push local governments to take more steps to cut air, water and soil pollution, but those efforts are proving difficult against longstanding local protectionism of key industries and local government ties to concessions for new projects.

.

To: Anderson, Neil[Anderson.Neil@epa.gov]
From: BNA Highlights
Sent: Tue 5/3/2016 2:02:25 AM
Subject: May 3 -- BNA, Inc. Daily Environment Report

Tuesday, May 3, 2016 · Number 85

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NEWS

Air Pollution
2008 Ozone Levels Met for Six Areas After Extension
Six areas will be able to demonstrate attainment with the 2008 ozone standards after receiving a one-year compliance extension from the Environmental Protection Agency, state and local air quality officials told Bloomberg BNA....

Asbestos
'Inevitable Use' With Asbestos Exposed Maker to Liability
Industrial machinery maker Hennessy Industries may be liable for an auto mechanic's death because its brake shoe machines would release asbestos dust when used to grind asbestos-based brake linings (Hetzel v. Hennessy Indus., Inc.,...

Chemicals
EPA's Children's Health Advisers to Meet
The Children's Health Protection Advisory Committee, which advises the Environmental Protection Agency, will meet May 24-25, the agency will announce in a Federal Register notice set for publication May 3. Details about the committee's...

Chemicals
EPA Expands Regions' Chemical Management Role
The Environmental Protection Agency is directing its regional offices to actively manage chemicals more than they traditionally have done. ...

Climate Change
California's Brown Feuds With Florida's Scott on Climate
It started out as a fight about which state had a better business climate, but then California Gov. Jerry Brown (D) shifted directions to skewer Florida Gov. Rick Scott (R) for refusing to act on

climate change. ...

Climate Policy
Navy Climate Program Questions Contractors on Carbon Emissions
Defense contractors hoping to continue selling their ships and planes to the U.S. Navy may soon need to reduce their carbon footprints....

Climate Regulation
EPA Defends Carbon Capture in Power Plant Rule
The Environmental Protection Agency is defending the availability of carbon capture systems despite initial technical difficulties at a Canadian power plant using the emissions control, denying five petitions to administratively reconsider...

Coal Mining
Interior Department Approves NW Colorado Mine Expansion
The Office of Surface Mining Reclamation and Enforcement has issued an approved mining plan to allow continued mining and production of up to 2.6 million tons of coal per year from two federal coal leases near Craig, Colo....

Corporate Responsibility
Big Funds Ignoring Climate Risks Rose Despite Warning
The number of big investors ignoring climate change risk increased last year despite a stark warning from Bank of England Governor Mark Carney's about the potential for "huge" losses from a sudden shift in regulation designed...

Drinking Water
Obama Flint Visit Unlikely to Yield Aid: Earnest
President Barack Obama is unlikely to announce during his upcoming Flint, Mich., visit "a new package of relief" for the city battling a drinking water crisis, the White House press secretary said May 2....

Drinking Water
Utilities Face Rule Hurdles in Water Technology: GAO
Water utilities often need to overcome financial and regulatory hurdles when considering and implementing technology to increase water supply or to improve the efficiency of their distribution system, a recent Government Accountability...

Emissions Trading
Maine Legislature Overrides Veto on RGGI Fund Redistribution
Maine lawmakers overrode a governor's veto and passed legislation (P.L. Chap. 498) that will deliver more energy efficiency funds to businesses....

Endangered Species
Interior Appeals Decision on Prairie Chicken Listing
The Interior Department is appealing a federal court decision that overturned a U.S. Fish and Wildlife Service decision to list the lesser prairie chicken as a threatened species (Permian Basin Petroleum Ass'n v. Interior, W. Tex., No....

Energy
Canada Plans Tougher Efficiency Rules for Some Products
Canada is proposing new energy efficiency standards for 15 products, such as microwave ovens, small electric motors and walk-in coolers and freezers, and more stringent standards for 20 products that already are regulated....

Energy

[DOE Aims to Increase Efficiency of Air Compressors]

The Energy Department is looking into increasing the energy efficiency of air and natural gas compressors, according to an April 29 pre-publication proposed rule. The proposed standards correspond to trial standard level (TSL) 2, which...

Energy

[DOE to Award $25 Million to Integrate Solar Into Grid]

The Energy Department announced $25 million in funding availability for software developers, solar companies and utilities to develop technologies to connect solar resources onto the nation's electric grid. The May 2 funding announcement,...

Hydraulic Fracturing

[Advisory Board to Review Hydraulic Fracturing Report]

The Chartered Science Advisory Board will review on June 14-15 a draft critique of the Environmental Protection Agency's draft assessment of hydraulic fracturing and its potential impacts on drinking water resources, the EPA will announce...

Hydraulic Fracturing

[Colorado Supreme Court Says Local Fracking Bans Preempted]

Colorado's oil and gas law preempts local bans on hydraulic fracturing in Longmont and Fort Collins, the state Supreme Court ruled in separate decisions May 2 (City of Longmont v. Colo. Oil and Gas Ass'n, Colo., No. 15-SC-667, 5/2/16,...

Natural Gas

[Utility Grab for Gas in Ground Hits Resistance by Regulators]

Utility owners seeking to buy natural gas fields while prices are cheap are having a tough time winning over state officials who worry that customers will pay the price if the bets go wrong....

Oil & Gas

[G-7 to Support Energy Investments Amid Oil Crash]

The Group of Seven countries will promote investing in energy projects through the oil price crash to ensure a steady stream of supply, ministers from the member countries said May 2....

Oil & Gas

[Toxic Tort Suit Halted During Cleanup]

A landowner's toxic tort suit against the owner of a leaking underground storage tank can't proceed while the state environmental department is overseeing cleanup, a Michigan appeals court affirmed (Carson City Hosp. v. Quick-Sav...

Oil Spills

[BP Investors Denied 'Pre-Spill' Certification]

The U.S. Supreme Court May 2 declined to review a federal appeals court's refusal to certify a "pre-spill class" of investors claiming BP PLC made material misstatements regarding the disastrous 2010 Deepwater Horizon oil spill...

Pesticides

[EPA Panel Finds Glyphosate Not Likely to Cause Cancer]

Glyphosate, a weed killer developed by Monsanto that is now the most widely used pesticide in the U.S., likely does not cause cancer, according to an Environmental Protection Agency review panel....

Pesticides

[Monsanto Gets Partial Victory in Roundup Litigation]

Monsanto won a partial victory in litigation over its Roundup herbicide when the Southern District of California ruled April 29 that some product liability claims of a cancer-stricken turf installer must be dismissed (Giglio v. Monsanto...

Radioactive Waste
Appeals Court License Decision Relevant to Storage Case: NRC
Nuclear Regulatory Commission Solicitor Andrew Averbach on May 2 pointed to a recent federal appeals court denial of a nuclear plant license intervention to further advance the agency's argument in defense of its final rule on radioactive...

Superfund
Ringwood Superfund Site Plan Sparks Petition
Residents of a mountain community northwest of New York City where Ford Motor Co. once dumped paint sludge are trying to override the borough's plans to pave over the dump and turn it into a recycling center, amassing nearly 500 signatures...

Sustainability
SEC Disclosure Project Takes Sustainability Bent
U.S. securities regulators are taking a fresh look at environmental, social and governance information included in corporate filings after receiving feedback that current disclosures on areas such as climate change and political spending...

Toxic Substances
Canada Imposes Conditions on Form of Propanaminium
Environment Canada imposed restrictions on a form of propanaminium for use in consumer products such as shampoos and cleaning products over concerns that the substance is toxic or could become toxic. The restrictions respond to notification...

Toxic Substances
Canada Takes No Regulatory Action on Heavy Fuel Oils
Canada will take no regulatory action related to nine substances—seven heavy fuel oils, the crude oil derivative ethylbenzene and the chemical intermediate hexachloroethane—based on environmental assessments concluding...

Water Pollution
EPA Needs to Report Benefits of Green Projects, OIG Says
The Environmental Protection Agency needs a process to routinely assess and report the environmental and economic benefits of energy and water efficiency, green infrastructure and environmentally innovative projects that have been funded...

Water Resources
Maine Will Appeal Penobscot Nation River Rights Case
Maine filed notice that it will cross appeal in a federal district court case concerning the boundaries of the Penobscot Indian Nation, particularly as they relate to the Penobscot River and rights to its water (Penobscot Nation v. Mills, D....

SPECIAL REPORT

Coal Mining
Advocates Take New Approach to Coal Bankruptcies
As bankruptcies continue to rock the coal sector, environmental groups are turning up the pressure on the Interior Department to either reexamine or stop altogether the practice of self-bonding,

including making unprecedented use of a complaint...

REGULATORY AGENDA

Comment Deadlines

MAY 2 FEDERAL REGISTER

MAY 3 FEDERAL REGISTER

To: Anderson, Neil[Anderson.Neil@epa.gov]
From: BNA Highlights
Sent: Mon 5/2/2016 8:05:02 PM
Subject: May 2 -- BNA, Inc. Daily Environment Report - Afternoon Briefing

Afternoon Briefing - Your Preview of Today's News

The following news provides a snapshot of what Bloomberg BNA is working on today. Read the full version of all the stories in the final issue, published each night.

EPA Directs Regions to Play Active Chemicals Management Role

Posted May 02, 2016, 12:54 P.M. ET

By Pat Rizzuto

The Environmental Protection Agency headquarters is directing regional offices to actively manage chemicals more than they have ever done.

“The new regional role is a significant change as the regions did not previously have much of a role in the Toxic Substances Control Act other than things like new chemicals enforcement and management of lead and PCBs,” said Charles Auer, a consultant with Charles Auer & Associates LLC who directed EPA's chemicals office for much of his 32-year career at the agency.

The EPA posted on April 29 an addendum revising National Program Managers guidance issued in 2015. The addendum guides managers as to what chemical and related issues they should focus on for the rest of this fiscal year, which ends Sept. 30., and FY 2017.

Regions are to let public health, local officials and other interested parties know the results of risk assessments the agency completes and work with such parties to manage high-priority chemicals.

Regional offices must let headquarters know about their chemical risk-reduction activities this year, the amended guidance said. Previously, such work was optional.

EPA Denies Reconsideration of New Power Plant Carbon Rule

Posted May 02, 2016, 12:31 P.M. ET

By Andrew Childers

The Environmental Protection Agency today denied five petitions to administratively reconsider its carbon dioxide standards for new and modified power plants, but the agency said it is deferring action on a sixth petition seeking to reconsider how biogenic carbon is treated under the rule.

The Utility Air Regulatory Group, American Electric Power, Ameren Corp., the Energy and Environmental Legal Institute and Wisconsin had all sought reconsideration of the new source performance standards for carbon dioxide emissions from new and modified power plants (RIN 2060-AQ91), arguing the carbon capture technology required for new coal-fired units is not adequately demonstrated based on technical challenges and cost overruns at the SaskPower Boundary Dam in Canada. The petitions had also challenged the EPA's methodology for determining baseline emissions from regulated power plants and the agency's outreach to environmental advocacy groups.

In an explanation of its denial, the EPA said that the challenges were unfounded or the issues were not raised in a timely manner.

The EPA said it has not yet taken action on a separate petition from the Biogenic CO2 Coalition, which had sought reconsideration of how the rule treats biogenic carbon, an issue also raised by Wisconsin.

Michigan Governor Seeks Flint Meeting with Obama

Posted May 02, 2016, 12:19 P.M. ET

By Rachel Leven

Michigan Gov. Rick Snyder (R) has requested a meeting this week with President Barack Obama and Flint, Mich., Mayor Karen Weaver to discuss the city's drinking water crisis, he said at a news conference today.

Snyder said today that he is waiting to receive a response. Obama is scheduled to visit Flint on Wednesday.

The governor, who said he is drinking filtered Flint water to show it is safe, said he wants to open a dialogue with the president on “how can we all work together to make Flint a better, stronger community and address the water problem as much as possible.”

Flint citizens still must drink bottled or filtered water and Snyder declined to offer a time frame for when citizens can expect to drink nonfiltered water. There is a flushing program ongoing in Flint and the city's water will be tested later this month, Snyder said, adding that lead service line removal is also part of the solution.

President Unlikely to Announce Aid in Flint: Earnest

Posted May 02, 2016, 3:36 P.M. ET

By Rachel Leven

President Barack Obama is unlikely to announce during his Flint, Mich., visit on Wednesday “a new package of relief” for the city battling a drinking water crisis, the White House press secretary said today.

“Obviously, there's been a significant commitment of resources to try to help the people of Flint in this urgent situation,” press secretary Josh Earnest told reporters, adding that Congress must send resources to Flint. Aid language has been on the table in Congress for months without success but has mostly recently been tacked onto a Senate water resources bill (S. 2848) that is set for floor consideration.

The president is also unlikely to delve into specific accountability for the crisis, beyond making “a forceful case that as the president, he feels responsible for the safety and well-being of every American,” Earnest said. The press secretary added that Michigan Gov. Rick Snyder (R) has received the traditional invitation as governor to meet the president on the tarmac in his state, following Snyder's earlier comments that he has requested a meeting with Obama.

“Governor Snyder, to his credit, has recognized that there is an important role for the state to play in helping the citizens of Flint recover,” Earnest said, stating that he was unsure whether a more in-depth meeting with Snyder would occur. “[T]his is a situation that should transcend political. This should be an opportunity for Democrats and Republicans to come together and try to right many of the wrongs that have been sustained by the citizens of Flint.”

Monsanto Weed Killer Glyphosate Not Carcinogenic: EPA

Posted May 02, 2016, 11:55 A.M. ET

By David Schultz

A cancer review committee at the Environmental Protection Agency has determined that glyphosate, Monsanto's signature weed killing chemical that is one of the most used pesticides in the world, is likely not a carcinogen.

The committee's final report, released online late Friday, reaches the opposite conclusion of a report from a year ago by the cancer research arm of the World Health Organization. That finding, that glyphosate is a likely carcinogen, had widespread ramifications—from increased regulatory actions in some states to new product liability lawsuits against Monsanto.

In its own report, the EPA's Cancer Assessment Review Committee determined that the WHO's review of scientific studies on glyphosate was skewed because it failed to take into account studies that reported no observable results.

Colorado Supreme Court Says Local Fracking Bans Preempted

Posted May 02, 2016, 1:59 P.M. ET

By Tripp Baltz

The Colorado Supreme Court today said in two separate rulings that a hydraulic fracturing ban in Longmont and a five-year moratorium in Fort Collins are preempted by state law and are therefore "invalid and unenforceable" (City of Longmont v. Colo. Oil and Gas Ass'n, Colo., No. 15SC667, 5/2/16; City of Fort Collins v. Colo. Oil and Gas Ass'n, Colo., No. 15SC668, 5/2/16).

The court, in a 19-page ruling May 2 on Fort Collins's voter-approved moratorium, said oil and gas drilling "is a matter of mixed state and local concern and, therefore, is subject to preemption by state law." The court said the five-year moratorium "operationally conflicts with the effectuation of state law." It made a similar ruling in a 29-page opinion about a voter-approved fracking ban in Longmont.

The two decisions affirm a Larimer County district court's ruling invalidating the Fort Collins moratorium on fracking and the storage of fracking waste in the city and a Boulder County district court's ruling invalidating the Longmont ban. The court remanded both cases for further proceedings consistent with its decisions.

EPA Needs to Report Benefits of Green Projects, OIG Says

Posted May 02, 2016, 3:09 P.M. ET

By Amena H. Saiyid

The Environmental Protection Agency needs a process to routinely collect and assess environmental and economic benefits of energy and water efficiency, green infrastructure and environmentally innovative projects that have been funded by the clean water state revolving fund, the agency's inspector general said today.

Between 2009 and 2014, the EPA awarded more than $12.7 billion in state revolving funds to states. Of that amount, $3.24 billion, or more than 25 percent, has funded green project reserve projects, or projects such as green infrastructure that yield sustainable solutions for wastewater infrastructure problems.

"Routine measurement and reporting of the benefits of completed projects can improve the EPA's ability to effectively oversee, manage and monitor the environmental and economic benefits of the substantial investment of $3.24 billion in public funds for GPR projects," the Inspector General said in "EPA Needs to Assess Environmental and Economic Benefits of Completed Clean Water State Revolving Fund Green Projects."

Since 2009, Congress has required that 20 percent of the funds appropriated for the clean water state revolving fund be set aside for the green project reserve fund that would finance projects that yield sustainable solutions for resolving wastewater infrastructure needs.

To: ona.maune@monsanto.com[ona.maune@monsanto.com]
Cc: Moriarty, Thomas[Moriarty.Thomas@epa.gov]; Anderson, Neil[Anderson.Neil@epa.gov]; Baris, Reuben[Baris.Reuben@epa.gov]
From: Nguyen, Khue
Sent: Thur 9/3/2015 5:54:46 PM
Subject: question re reg num 71995-25

Hi Ona,

We have not corresponded before. I manage the registration review process for glyphosate. Reuben told me that you are the correct contact for this question. We are looking at the label for reg number 71995-25 and trying to figure out the use rate in x lb ae/A. We noticed that the current stamped label does not specify the x lb ae/gal information for this product. Can you please provide that information to us? This is rather time-sensitive, so we would really appreciate a response soon.

Thanks!

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: Morton, Thurston
Location: HED Library
Importance: Normal
Subject: Glyphosate PRA
Start Date/Time: Wed 8/5/2015 1:30:00 PM
End Date/Time: Wed 8/5/2015 2:00:00 PM

Let's get together and talk about the glyphosate PRA and scope out the work needed between now and the end of Sept. The CARC is Sept 16 and the PRA will have to be finished soon after.

Tom can you send the latest version of the glyphosate PRA?

From: Bloem, Thomas
Location: DCRoomPYS9621/Potomac-Yard-One
Importance: Normal
Subject: Accepted: hold for: glyphosate call with Monsanto re inerts info request
Start Date/Time: Tue 4/5/2016 3:30:00 PM
End Date/Time: Tue 4/5/2016 4:30:00 PM

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Bloem, Thomas
Sent: Mon 11/2/2015 6:40:56 PM
Subject: glyphosate CARC

Jess

Glyphosate will be going to RARC this week and I need a copy of the CAR report to forward to them. Thanks.

Tom

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Bloem, Thomas
Sent: Tue 9/29/2015 12:08:33 PM
Subject: RE: Glyphosate PRA

Got it and I will tell you when we are done with the risk assessment.

From: Rowland, Jess
Sent: Tuesday, September 29, 2015 7:52 AM
To: Bloem, Thomas
Cc: Smith, Charles
Subject: Glyphosate PRA

Tom

Ex. 5 - Deliberative Process

Thanks

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Bloem, Thomas
Location: DCRoomPYS9100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: glyphosate: meeting with Monsanto
Start Date/Time: Thur 6/4/2015 5:00:00 PM
End Date/Time: Thur 6/4/2015 6:00:00 PM

From: Brunsman, Lori
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Glyphosate CARC Meeting
Start Date/Time: Wed 9/16/2015 1:30:00 PM
End Date/Time: Wed 9/16/2015 2:30:00 PM

From: Brunsman, Lori
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Glyphosate CARC Meeting
Start Date/Time: Wed 9/16/2015 4:30:00 PM
End Date/Time: Wed 9/16/2015 8:30:00 PM

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Kidwell, Jessica[kidwell.jessica@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Chen, Jonathan[Chen.Jonathan@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]
From: Kent, Ray
Sent: Wed 9/23/2015 3:59:40 PM
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

I'm in the office and I can't edit the file. It says "locked for editing by Lori Brunsman"…

From: Brunsman, Lori
Sent: Wednesday, September 23, 2015 11:48 AM
To: Kidwell, Jessica; Middleton, Karlyn; Akerman, Gregory; Lobdell, Danelle; Chen, Jonathan; Liccione, John; Wood, Charles; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

I think the problem must have to do with accessing Sharepoint from home. It works fine here at the office.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:48 AM
To: Middleton, Karlyn; Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Maybe there's some code in there preventing us from editing. I don't know.

From: Middleton, Karlyn
Sent: Wednesday, September 23, 2015 11:47 AM
To: Kidwell, Jessica; Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Not working.

From: Kidwell, Jessica
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This still doesn't work for me. Does it work for anyone else? If it's not working I'm going to take it down. Please let me know.

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:43 AM
To: Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Middleton, Karlyn; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
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To: Kidwell, Jessica[kidwell.jessica@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Chen, Jonathan[Chen.Jonathan@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]
From: Middleton, Karlyn
Sent: Wed 9/23/2015 3:49:05 PM
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

No circle.

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:48 AM
To: Brunsman, Lori; Akerman, Gregory; Lobdell, Danelle; Chen, Jonathan; Liccione, John; Wood, Charles; Middleton, Karlyn; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

You get the green circle when you save it?

From: Brunsman, Lori
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It works for me here at the office.

Have a great day!

Lori

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***Lori Brunsman, Statistician and Project Officer**
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Office of Pesticide Programs

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From: Kidwell, Jessica
Sent: Wed 9/23/2015 3:48:21 PM
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

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Sent: Wednesday, September 23, 2015 11:46 AM
To: Kidwell, Jessica; Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Middleton, Karlyn; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

This still doesn't work for me. Does it work for anyone else? If it's not working I'm going to take it down. Please let me know.

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:43 AM
To: Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Middleton, Karlyn; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Cc: Kidwell, Jessica
Subject: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Let's see if we're able to edit this version. This is Jess's file which has Cal's formatting edits. Please share this with anyone I missed on CARC.

Open Glyphosate CARC Final 9.21.15_cpr_JMK.docx

Followthis document to get updates in your newsfeed.

To: Kidwell, Jessica[kidwell.jessica@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]; Chen, Jonathan[Chen.Jonathan@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]
From: Middleton, Karlyn
Sent: Wed 9/23/2015 3:46:58 PM
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Not working.

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:46 AM
To: Kidwell, Jessica; Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Middleton, Karlyn; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

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Cc: Kidwell, Jessica
Subject: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

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To: Kidwell, Jessica[kidwell.jessica@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]; Chen, Jonathan[Chen.Jonathan@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]
From: Kidwell, Jessica
Sent: Wed 9/23/2015 3:46:04 PM
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

This still doesn't work for me. Does it work for anyone else? If it's not working I'm going to take it down. Please let me know.

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:43 AM
To: Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Middleton, Karlyn; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Cc: Kidwell, Jessica
Subject: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

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Open Glyphosate CARC Final 9.21.15_cpr_JMK.docx

Followthis document to get updates in your newsfeed.

To: Akerman, Gregory[Akerman.Gregory@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]; Chen, Jonathan[Chen.Jonathan@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]
Cc: Kidwell, Jessica[kidwell.jessica@epa.gov]
From: Kidwell, Jessica
Sent: Wed 9/23/2015 3:43:04 PM
Subject: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Let's see if we're able to edit this version. This is Jess's file which has Cal's formatting edits. Please share this with anyone I missed on CARC.

Open Glyphosate CARC Final 9.21.15_cpr_JMK.docx

Followthis document to get updates in your newsfeed.

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Chen, Jonathan
Sent: Tue 9/15/2015 7:45:18 PM
Subject: RE: Glyphosate CARC Package

Thank you.

Jonathan Chen

From: Brunsman, Lori
Sent: Tuesday, September 15, 2015 3:04 PM
To: Chen, Jonathan
Subject: RE: Glyphosate CARC Package

Jonathan –

There are a TON of documents. I will at least get the CARC package to you this afternoon and the rest of the documents to you tomorrow morning before the meeting.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Chen, Jonathan
Sent: Tuesday, September 15, 2015 2:55 PM
To: Brunsman, Lori
Subject: FW: Glyphosate CARC Package

Dear Lori:

Can you send me the documents? I cannot access the CARC packages from Lotus Note.

Jonathan Chen

From: Brunsman, Lori
Sent: Wednesday, September 09, 2015 1:58 PM
To: Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kent, Ray; Kidwell, Jessica; Liccione, John; McCarroll, Nancy; Middleton, Karlyn; OPP HED Notes Coordinators; Rowland, Jess; Shah, Pv; Woo, Yintak; Wood, Charles; Lobdell, Danelle; Morton, Thurston; Smith, Charles
Subject: Glyphosate CARC Package

The Glyphosate CARC package is now on the Lotus Notes database.

Please let me know if you cannot access it and I will email you the documents.

REMINDER: the Glyphosate CARC meeting is an **ALL-DAY** meeting (9:00 am to 4:00 pm) next **Wednesday, September 16, 2015**, in room S-10100.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Chen, Jonathan
Sent: Tue 9/15/2015 6:55:05 PM
Subject: FW: Glyphosate CARC Package

Dear Lori:

Can you send me the documents? I cannot access the CARC packages from Lotus Note.

Jonathan Chen

From: Brunsman, Lori
Sent: Wednesday, September 09, 2015 1:58 PM
To: Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kent, Ray; Kidwell, Jessica; Liccione, John; McCarroll, Nancy; Middleton, Karlyn; OPP HED Notes Coordinators; Rowland, Jess; Shah, Pv; Woo, Yintak; Wood, Charles; Lobdell, Danelle; Morton, Thurston; Smith, Charles
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Have a great day!

Lori

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Lori Brunsman, Statistician and Project Officer

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Environmental Protection Agency
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brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Wood, Charles
Sent: Thur 9/10/2015 1:08:50 PM
Subject: RE: Glyphosate DERs and Support Docs: Part 1 of 2

Thanks, Lori. Sorry for the trouble!

--Charles

From: Brunsman, Lori
Sent: Thursday, September 10, 2015 8:26 AM
To: Wood, Charles
Subject: Glyphosate DERs and Support Docs: Part 1 of 2

Charles –

There are a LOT of documents in the Glyphosate CARC package. I will send them to you in multiple emails.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
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Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

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One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Wood, Charles
Sent: Wednesday, September 09, 2015 3:08 PM
To: Brunsman, Lori
Subject: RE: Glyphosate CARC Package

Hi Lori,

Can you email me the package?

--Charles

From: Brunsman, Lori
Sent: Wednesday, September 09, 2015 1:58 PM
To: Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kent, Ray; Kidwell, Jessica; Liccione, John; McCarroll, Nancy; Middleton, Karlyn; OPP HED Notes Coordinators; Rowland, Jess; Shah, Pv; Woo, Yintak; Wood, Charles; Lobdell, Danelle; Morton, Thurston; Smith, Charles
Subject: Glyphosate CARC Package

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Please let me know if you cannot access it and I will email you the documents.

REMINDER: the Glyphosate CARC meeting is an **ALL-DAY** meeting (9:00 am to 4:00 pm) next **Wednesday, September 16, 2015**, in room S-10100.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
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brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Wood, Charles
Sent: Wed 9/9/2015 7:08:04 PM
Subject: RE: Glyphosate CARC Package

Hi Lori,

Can you email me the package?

--Charles

From: Brunsman, Lori
Sent: Wednesday, September 09, 2015 1:58 PM
To: Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kent, Ray; Kidwell, Jessica; Liccione, John; McCarroll, Nancy; Middleton, Karlyn; OPP HED Notes Coordinators; Rowland, Jess; Shah, Pv; Woo, Yintak; Wood, Charles; Lobdell, Danelle; Morton, Thurston; Smith, Charles
Subject: Glyphosate CARC Package

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Have a great day!

Lori

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brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]
From: Rowland, Jess
Sent: Wed 9/9/2015 12:56:08 PM
Subject: RE: reschedule Glyphosate CARC?

Do NOT reschedule. The documents will be out today. 1-week is enough.

Sent from my Windows Phone

From: Brunsman, Lori
Sent: 9/9/2015 7:31 AM
To: Schlosser, Christopher; Rowland, Jess; Middleton, Karlyn
Subject: reschedule Glyphosate CARC?

The Glyphosate meeting is currently scheduled for one week from today, September 16th. The CARC package was due out September 2nd. When the package is this late, we typically reschedule the meeting. Do you want me to reschedule Glyphosate? What day do you think we'll get the package?

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
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703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Davis, Donna
Sent: Wed 8/26/2015 3:14:46 PM
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Lori,

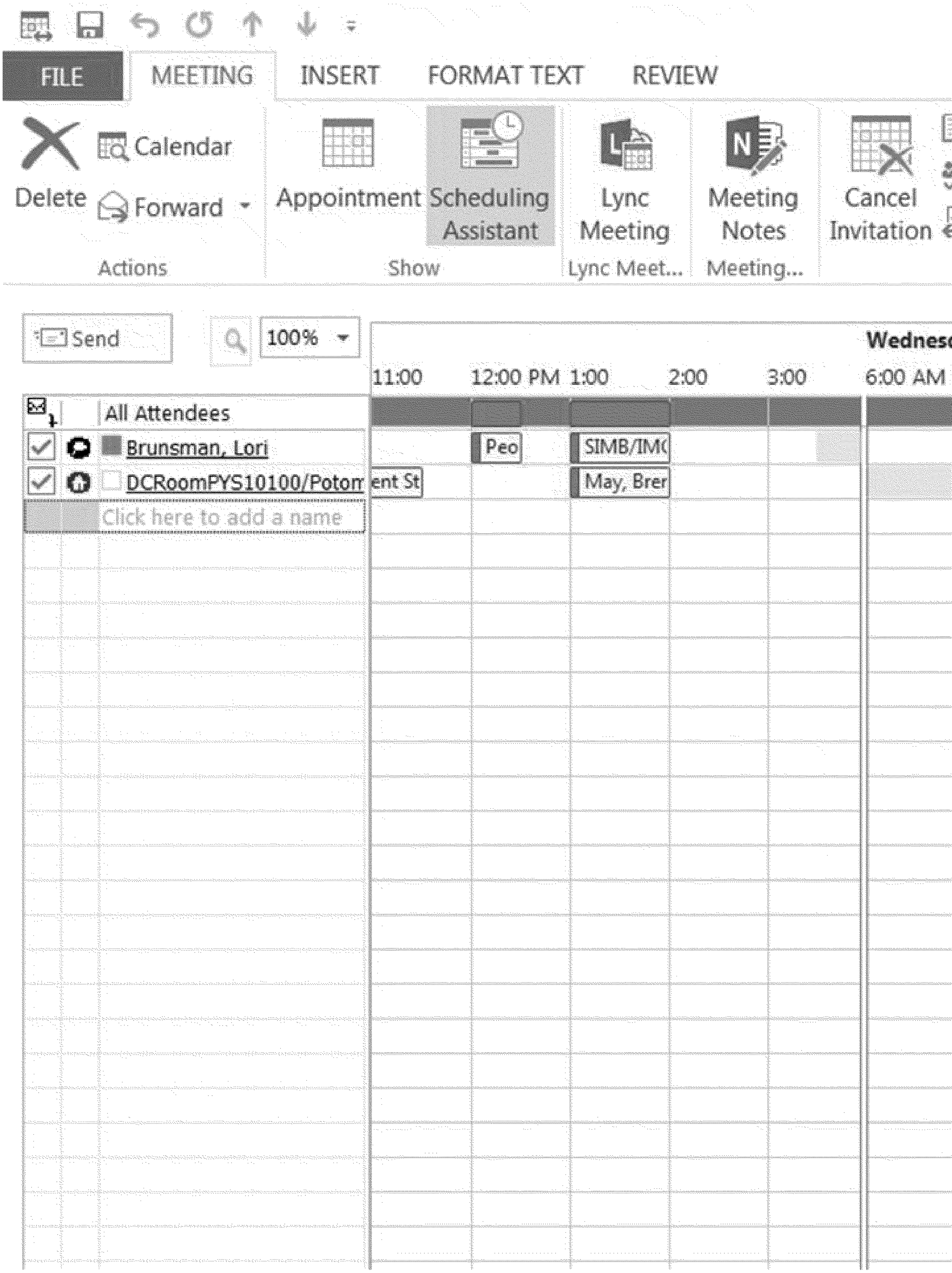
Must be left over from the old lotus notes days. I don't know what to tell you. I don't have a meeting on my calendar to cancel.

Donna

From: Brunsman, Lori
Sent: Wednesday, August 26, 2015 8:58 AM
To: Davis, Donna
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Donna –

Here's what I see for S-10100 with Outlook Calendar scheduling assistant for the 16th:


FILE
MEETING
INSERT
FORMAT TEXT
REVIEW
Delete
Calendar
Forward
Actions
Appointment
Scheduling Assistant
Show
Lync Meeting
Lync Meet...
Meeting Notes
Meeting...
Cancel Invitation
Send
100%
Wednes
11:00
12:00 PM
1:00
2:00
3:00
6:00 AM
All Attendees
Brunsman, Lori
DCRoomPYS10100/Potom
Click here to add a name
Peo
SIMB/IMC
ent St
May, Bren

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Davis, Donna
Sent: Wednesday, August 26, 2015 8:28 AM
To: Brunsman, Lori
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Lori,

I don't have an 8:30 – 9:30 slot reserved in 10100 for ChemSAC. My calendar doesn't show anything….

Donna

From: Brunsman, Lori
Sent: Wednesday, August 26, 2015 7:07 AM
To: Davis, Donna
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Donna –

Thank you for releasing the room reservation for S-10100 on 9/16/15. However, you released the 9:30-10:30 time slot, but not the 8:30-9:30 time slot. The Glyphosate CARC meeting starts at 9:00. If you could please release that earlier room reservation, too, I'd appreciate it.

Thanks!

Have a great day!

Lori

****

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brunsman.lori@epa.gov
703-308-2902

From: Davis, Donna
Sent: Tuesday, August 25, 2015 1:52 PM
To: Brunsman, Lori; Keller, Nancy
Cc: Wilbur, Donald; VanAlstine, Julie; Morton, Thurston; Rowland, Jess
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Lori,

We were planning to meet and were doing a big training session in the room. Sounds like Jess is going to trump us. I will tell the co-chairs that we have been displaced. We may have to delay our training.

Donna

From: Brunsman, Lori
Sent: Tuesday, August 25, 2015 8:44 AM
To: Davis, Donna; Keller, Nancy
Subject: CARC needs S-10100 on 9/16/15 all day

Donna and Nancy –

We are having a marathon CARC meeting on Glyphosate all day (9:00 am – 4:00 pm) on Wednesday, September 16. I see that you have room S-10100 reserved for part of that day. Are you still having meetings on that day and, if so, would it be possible for you to move your meetings to another meeting room on that day?

Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
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brunsman.lori@epa.gov
703-308-2902

From: Shah, Pv
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Declined: Glyphosate CARC Meeting
Start Date/Time: Wed 9/16/2015 2:30:00 PM
End Date/Time: Wed 9/16/2015 4:30:00 PM

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Davis, Donna
Sent: Wed 8/26/2015 12:28:27 PM
Subject: RE: CARC needs S-10100 on 9/16/15 all day

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703-308-2902

From: Davis, Donna
Sent: Tuesday, August 25, 2015 1:52 PM
To: Brunsman, Lori; Keller, Nancy
Cc: Wilbur, Donald; VanAlstine, Julie; Morton, Thurston; Rowland, Jess
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Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
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One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Rowland, Jess
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 9/16/2015 4:30:00 PM
End Date/Time: Wed 9/16/2015 8:30:00 PM

From: Rowland, Jess
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 9/16/2015 2:30:00 PM
End Date/Time: Wed 9/16/2015 4:30:00 PM

From: DCRoomPYS10100/Potomac-Yard-One
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 9/16/2015 2:30:00 PM
End Date/Time: Wed 9/16/2015 4:30:00 PM

Your request was accepted.

Sent by Microsoft Exchange Server 2016

From: DCRoomPYS10100/Potomac-Yard-One
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 9/16/2015 1:30:00 PM
End Date/Time: Wed 9/16/2015 2:30:00 PM

Your request was accepted.

Sent by Microsoft Exchange Server 2016

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Keller, Nancy[Keller.Nancy@epa.gov]
Cc: Wilbur, Donald[Wilbur.Donald@epa.gov]; VanAlstine, Julie[VanAlstine.Julie@epa.gov]; Morton, Thurston[Morton.Thurston@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]
From: Davis, Donna
Sent: Tue 8/25/2015 5:52:27 PM
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Lori,

We were planning to meet and were doing a big training session in the room. Sounds like Jess is going to trump us. I will tell the co-chairs that we have been displaced. We may have to delay our training.

Donna

From: Brunsman, Lori
Sent: Tuesday, August 25, 2015 8:44 AM
To: Davis, Donna; Keller, Nancy
Subject: CARC needs S-10100 on 9/16/15 all day

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Thanks!

Have a great day!

Lori

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brunsman.lori@epa.gov
703-308-2902

From: DCRoomPYS10100/Potomac-Yard-One
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 9/16/2015 4:30:00 PM
End Date/Time: Wed 9/16/2015 8:30:00 PM

Your request was accepted.

Sent by Microsoft Exchange Server 2016

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Keller, Nancy
Sent: Tue 8/25/2015 5:42:46 PM
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Sorry, I just released it.

Nancy J. Keller (Tsaur)
Risk Assessment Branch 3 (RAB3)
Health Effects Division
Office of Pesticide Programs
keller.nancy@epa.gov
703-603-8905

From: Brunsman, Lori
Sent: Tuesday, August 25, 2015 1:36 PM
To: Keller, Nancy
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Nancy –

Did you forget to release S-10100 on 9/16/15? Outlook Calendar still shows you have it reserved for the afternoon.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Keller, Nancy
Sent: Tuesday, August 25, 2015 10:49 AM
To: Brunsman, Lori; Davis, Donna
Cc: Smith, Charles; Rowland, Jess
Subject: RE: CARC needs S-10100 on 9/16/15 all day

No problem, I will release the room on 9/16.

Thanks!

Nancy J. Keller (Tsaur)
Risk Assessment Branch 3 (RAB3)
Health Effects Division
Office of Pesticide Programs
keller.nancy@epa.gov
703-603-8905

From: Brunsman, Lori
Sent: Tuesday, August 25, 2015 10:26 AM
To: Keller, Nancy; Davis, Donna
Cc: Smith, Charles; Rowland, Jess
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Nancy –

Jess set-up the all-day Glyphosate meeting on September 16th with the CARC members and other critical attendees, and told everybody we would meet in S-10100, but forgot to check if S-10100 was actually available during the entirety of the 9:00 am to 4:00 pm timeslot needed for this meeting.

I believe the CARC meeting that day will be an HED priority over the RARC meeting. If you could find another room for the RARC, I would appreciate it.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Keller, Nancy
Sent: Tuesday, August 25, 2015 9:24 AM
To: Brunsman, Lori; Davis, Donna
Cc: Smith, Charles
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Yes, as of this moment, we have a RARC meeting scheduled for 1-3 pm (endothall).

The decision to cancel RARC is not made until the day before the RARC meeting, so I cannot be certain whether or not we definitely need the room…

I prefer to keep 10100 but if the CARC meeting is an HED priority over RARC, then I can find another room.

Nancy J. Keller (Tsaur)
Risk Assessment Branch 3 (RAB3)
Health Effects Division
Office of Pesticide Programs
keller.nancy@epa.gov
703-603-8905

From: Brunsman, Lori
Sent: Tuesday, August 25, 2015 8:44 AM
To: Davis, Donna; Keller, Nancy
Subject: CARC needs S-10100 on 9/16/15 all day

Donna and Nancy –

We are having a marathon CARC meeting on Glyphosate all day (9:00 am – 4:00 pm) on Wednesday, September 16. I see that you have room S-10100 reserved for part of that day. Are you still having meetings on that day and, if so, would it be possible for you to move your meetings to another meeting room on that day?

Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer

Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Davis, Donna[Davis.Donna@epa.gov]
Cc: Smith, Charles[Smith.Charles@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]
From: Keller, Nancy
Sent: Tue 8/25/2015 2:48:45 PM
Subject: RE: CARC needs S-10100 on 9/16/15 all day

No problem, I will release the room on 9/16.

Thanks!

Nancy J. Keller (Tsaur)
Risk Assessment Branch 3 (RAB3)
Health Effects Division
Office of Pesticide Programs
keller.nancy@epa.gov
703-603-8905

From: Brunsman, Lori
Sent: Tuesday, August 25, 2015 10:26 AM
To: Keller, Nancy; Davis, Donna
Cc: Smith, Charles; Rowland, Jess
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Nancy –

Jess set-up the all-day Glyphosate meeting on September 16th with the CARC members and other critical attendees, and told everybody we would meet in S-10100, but forgot to check if S-10100 was actually available during the entirety of the 9:00 am to 4:00 pm timeslot needed for this meeting.

I believe the CARC meeting that day will be an HED priority over the RARC meeting. If you could find another room for the RARC, I would appreciate it.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Keller, Nancy
Sent: Tuesday, August 25, 2015 9:24 AM
To: Brunsman, Lori; Davis, Donna
Cc: Smith, Charles
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Yes, as of this moment, we have a RARC meeting scheduled for 1-3 pm (endothall).

The decision to cancel RARC is not made until the day before the RARC meeting, so I cannot be certain whether or not we definitely need the room…

I prefer to keep 10100 but if the CARC meeting is an HED priority over RARC, then I can find another room.

Nancy J. Keller (Tsaur)
Risk Assessment Branch 3 (RAB3)
Health Effects Division
Office of Pesticide Programs
keller.nancy@epa.gov
703-603-8905

From: Brunsman, Lori
Sent: Tuesday, August 25, 2015 8:44 AM
To: Davis, Donna; Keller, Nancy
Subject: CARC needs S-10100 on 9/16/15 all day

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Thanks!

Have a great day!

Lori

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Lori Brunsman, Statistician and Project Officer
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Health Effects Division
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Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Davis, Donna[Davis.Donna@epa.gov]
Cc: Smith, Charles[Smith.Charles@epa.gov]
From: Keller, Nancy
Sent: Tue 8/25/2015 1:24:04 PM
Subject: RE: CARC needs S-10100 on 9/16/15 all day

Yes, as of this moment, we have a RARC meeting scheduled for 1-3 pm (endothall).

The decision to cancel RARC is not made until the day before the RARC meeting, so I cannot be certain whether or not we definitely need the room…

I prefer to keep 10100 but if the CARC meeting is an HED priority over RARC, then I can find another room.

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keller.nancy@epa.gov
703-603-8905

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Thanks!

Have a great day!

Lori

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Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

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Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Middleton, Karlyn
Sent: Thur 8/13/2015 6:58:19 PM
Subject: RE: FY 15 Accomplishments

Thanks Lori!

From: Brunsman, Lori
Sent: Thursday, August 13, 2015 7:13 AM
To: Middleton, Karlyn
Subject: RE: FY 15 Accomplishments

Sure!

In FY15:

CARC: 4 peer review meetings on 4 chemicals for cancer classification by the CARC (the last of these 4 meetings is Glyphosate on 9/16/15)

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Middleton, Karlyn
Sent: Wednesday, August 12, 2015 3:46 PM
To: Brunsman, Lori
Cc: Rowland, Jess
Subject: FW: FY 15 Accomplishments

Hi Lori,

Can you pull this together for the CARC meetings last fiscal year? See last year highlighted. Thank you!

From: Smith, Charles
Sent: Tuesday, August 11, 2015 12:52 PM
To: Olinger, Christine; Dawson, Jeffrey; Shelat, Shalu; Rury, Kristin; Perron, Monique; Middleton, Karlyn; Reaves, Elissa; Mendez, Elizabeth; Davis, Donna; Wilbur, Donald; VanAlstine, Julie; Morton, Thurston; Piper, Sheila; Kidwell, Jessica; Dunbar, Anwar; Lowit, Anna; Britton, Wade; Lowe, Kelly
Cc: Vogel, Dana; Rowland, Jess
Subject: FY 15 Accomplishments

All,

The HED management team is working on HED's FY 15 accomplishments. As part of that work, we are trying to put together a list of the SAC/SARC meetings that have occurred throughout the year. I have copied below what we put into last year's accomplishments document. I am hoping that those involved with each SAC/SARC can provide some similar brief write-up for FY 15. I need this done by no later than noon next Monday (8/17). If you have any questions, please feel free to let me know. Thanks!

SAC/SARC Meetings:

- ExpoSAC: 30 peer review meetings on various technical issues as well as for review of occupational and residential exposure assessments produced in support of risk assessment. State pesticide representatives were invited to 6 of these meetings and ExpoSAC members had open discussions with these representatives about various occupational and residential exposure issues they were dealing with in their individual states.

- ToxSAC: 31 peer review meetings for endpoint selection or protocol reviews in support of risk assessment. Including 4 new active ingredients (Halauxifen-methyl, Bicyclopyrone, Solatenol, Momfluorthrin), 7 OPs (Acephate, Pirimiphos-methyl, Malathion, Terbufos, Chlorethoxyfos, Diazinon, Ethoprop), which updated BMD modeling and steady state assessments for Registration Review, as well as other chemicals in support of Registration Review.

- ChemSAC: 21 Meetings on various issues as well as technical review of residue chemistry documents. Development of science policy on processed commodities. Provide training to branch chemists. Included PMRA and IR-4 in multiple meetings.

- DESAC: 15 meetings on various issues along with detailed review of probabilistic dietary assessments (Dicrotophos, Thiabendazole, Prallethrin, Chlorpyrifos, Deltamethrin, etc.) and training of the new RDF generator program, USDA PDP Monitoring Program, and manual creation of RDFs for use in acute probabilistic assessments. In addition, there were 3 training sessions on the use of Calendex for steady state dietary assessments, a Commodity Specific Analysis refresher training, and a discussion about the new DEEM User Guide. The SAC also met twice to discuss the processing factors table that was developed by the ChemSAC Processing Factors Focus Group and provided feedback on the "Summary of EPA's Uncertainty and Variability Data Call Responses" document.

- ROCKS: 8 meetings (Flupyradifurone; Halauxifen-methyl; Benzovindiflupyr; Terbufos; Tricyclazole (e-review); Isofetamid; Benalaxyl-M; Bicyclopyrone). Several Co-chair consultations

- CARC: 10 peer review meetings on 11 chemicals for cancer classification by the CARC

- DART: 4 DART meetings related to dose selection for rat and/or mouse carcinogenicity and immunotoxicity studies

- HASPOC: HASPOC reviewed data waivers for 86 chemicals for a variety of toxicity studies, primarily for the acute and subchronic neurotoxicity, subchronic inhalation studies, and immunotoxicity studies. Waivers were granted for 51 of the 57 requests for a subchronic inhalation studies resulting in the savings of approximately 4000 animals and $4 million, the cost of conducting these studies. Similarly, waivers were granted for 31 of the 35 requests for the neurotoxicity studies, resulting the saving of approximately 5000 animals and $5 million, the cost of conducting these studies. Finally, waivers were granted for 46 of the 49 requests for immunotoxicity studies, resulting the saving of approximately 750 animals and $3 million, the cost of conducting these studies.

•□□□□□□ RARC: The RARC reviewed 15 risk assessments: 4 new active ingredients (tricyclazole; fluensulfone; halauxifen-methyl; isofetamid); 1 first food use (flupyradifurone); 6 Registration Review Risk Assessments (hydrogen cyanamide; cyromazine; dicrotophos; clethodim; chlorfenapyr; tebuthiuron;); 1 pre-RARC meeting (flupyradifurone);1 e-review (flutolanil); and 2 other assessments (Prallethrin (label amendment for mosquitocide use); deltamethrin (tolerance without US registration for use on finfish).

Charles " Billy" Smith

Branch Chief RAB4

Health Effects Division

Office of Pesticide Programs

703-305-0291

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Rowland, Jess
Sent: Wed 8/12/2015 1:26:19 AM
Subject: RE: any new Glyphosate data that needs stats?

No

Sent from my Windows Phone

From: Brunsman, Lori
Sent: 8/11/2015 2:12 PM
To: Rowland, Jess
Subject: any new Glyphosate data that needs stats?

Jess –

Just wondering if any of the new Glyphosate data will need stats before the September 16th CARC.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Lobdell, Danelle
Sent: Wed 6/17/2015 6:20:02 PM
Subject: Re: Glyphosate CARC Meeting

Thank you

Sent from my iPhone

On Jun 17, 2015, at 11:18 AM, Brunsman, Lori <Brunsman.Lori@epa.gov> wrote:

Danelle –

The CARC meeting on Glyphosate has been cancelled. No CARC meeting will be held.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Lobdell, Danelle
Sent: Wednesday, June 10, 2015 4:31 PM
To: Brunsman, Lori
Subject: RE: Glyphosate CARC Meeting

Hi Lori,

Can you send a new updated invite for this meeting? You deleted the previous invite (which did update for July 8th) and it is now off of my calendar.

Thank you,

Danelle

Danelle T. Lobdell, Ph.D., M.S.

Epidemiologist

National Health and Environmental Effects Research Laboratory

Environmental Public Health Division

Mail:

USEPA

MD 58A

Research Triangle Park, NC 27711

Package Delivery:

USEPA Human Studies Facility

104 Mason Farm Rd, Room 52

Chapel Hill, NC 27514-4512

Phone: 919-843-4434 Fax: 919-966-7584

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv

Subject: Glyphosate CARC Meeting

We are considering moving the CARC meeting on Glyphosate from June 24th to July 8th. Please let me know ASAP if you CANNOT make the July 8th meeting date.

Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Lobdell, Danelle
Sent: Wed 6/10/2015 8:31:00 PM
Subject: RE: Glyphosate CARC Meeting

Hi Lori,

Can you send a new updated invite for this meeting? You deleted the previous invite (which did update for July 8th) and it is now off of my calendar.

Thank you,

Danelle

Danelle T. Lobdell, Ph.D., M.S.

Epidemiologist

National Health and Environmental Effects Research Laboratory

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Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
Subject: Glyphosate CARC Meeting

We are considering moving the CARC meeting on Glyphosate from June 24th to July 8th. Please let me know ASAP if you CANNOT make the July 8th meeting date.

Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Rowland, Jess
Sent: Tue 6/2/2015 2:11:49 PM
Subject: Glyphosate

Hi Lori
Please cancel the Glyphosate CARC meeting.
Thanks
JR
Sent from my Windows Phone

From: Kidwell, Jessica
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

From: Rowland, Jess
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

From: Wood, Charles
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

From: Dunbar, Anwar
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

From: Middleton, Karlyn
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

From: Shah, Pv
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

From: Kent, Ray
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Kent, Ray
Sent: Tue 5/26/2015 5:53:55 PM
Subject: RE: Glyphosate male mouse stats

Thanks, Lori…

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 1:38 PM
To: Kent, Ray
Subject: Glyphosate male mouse stats

Ray –

Attached are the Glyphosate male mouse hemangiosarcoma stats that will be presented at the CARC meeting on July 8th.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Lobdell, Danelle
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

From: McCarroll, Nancy
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

From: DCRoomPYS10100/Potomac-Yard-One
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 7/8/2015 2:30:00 PM
End Date/Time: Wed 7/8/2015 4:30:00 PM

Your request was accepted.

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Rowland, Jess
Sent: Tue 5/26/2015 5:47:43 PM
Subject: RE: Charles would likely miss Glyphosate CARC Meeting on July 8th

Thanks for this. Charles said he will find a Starbucks and call in from the beach. So pl go ahead and reschedule.

Sent from my Windows Phone

From: Brunsman, Lori
Sent: 5/26/2015 1:45 PM
To: Rowland, Jess
Subject: Charles would likely miss Glyphosate CARC Meeting on July 8th

Charles is the only person on the CARC who has indicated they could not make a meeting on July 8th.

Lori

From: Wood, Charles
Sent: Tuesday, May 26, 2015 9:59 AM
To: Brunsman, Lori
Cc: Rowland, Jess
Subject: RE: Glyphosate CARC Meeting

Hi Lori,

I will be traveling on Jul 8th and would likely miss a CARC meeting on that day.

--Charles

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv

Subject: Glyphosate CARC Meeting

We are considering moving the CARC meeting on Glyphosate from June 24th to July 8th. Please let me know ASAP if you CANNOT make the July 8th meeting date.

Thanks!

Have a great day!

Lori

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Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
Cc: Rowland, Jess[Rowland.Jess@epa.gov]
From: Wood, Charles
Sent: Tue 5/26/2015 1:59:16 PM
Subject: RE: Glyphosate CARC Meeting

Hi Lori,

I will be traveling on Jul 8th and would likely miss a CARC meeting on that day.

--Charles

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
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Thanks!

Have a great day!

Lori

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brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; OPP HED CARC[OPP_HED_CARC@epa.gov]; Christensen, Carol[Christensen.Carol@epa.gov]; Sarkar, Bayazid[Sarkar.Bayazid@epa.gov]; Shah, Aruna[Shah.Aruna@epa.gov]; Tao, Jenny[Tao.Jenny@epa.gov]; Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Miller, David[Miller.DavidJ@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]
Cc: Kidwell, Jessica[kidwell.jessica@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Shah, Pv[Shah.Pv@epa.gov]
From: Chen, Jonathan
Sent: Tue 5/26/2015 1:55:50 PM
Subject: RE: Glyphosate CARC Meeting

July 8th is good for me.

Jonathan Chen

Jonathan Chen

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
Subject: Glyphosate CARC Meeting

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Thanks!

Have a great day!

Lori

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Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; OPP HED CARC[OPP_HED_CARC@epa.gov]; Christensen, Carol[Christensen.Carol@epa.gov]; Sarkar, Bayazid[Sarkar.Bayazid@epa.gov]; Shah, Aruna[Shah.Aruna@epa.gov]; Tao, Jenny[Tao.Jenny@epa.gov]; Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Miller, David[Miller.DavidJ@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]
Cc: Kidwell, Jessica[kidwell.jessica@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Shah, Pv[Shah.Pv@epa.gov]
From: Dunbar, Anwar
Sent: Tue 5/26/2015 1:54:45 PM
Subject: RE: Glyphosate CARC Meeting

That looks fine for me.

Anwar Y. Dunbar, Ph.D., Pharmacologist

Risk Assessment Branch 1

The Human Health Effects Division/ The Office of Pesticide Programs

1200 Pennsylvania Ave, NW

Washington, DC 20460

"Except for in the most unique of circumstances, mastery of any cognitively complex skill or task requires roughly 10,000 hours of practice"- Malcolm Gladwell, Author of the book Outliers

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
Subject: Glyphosate CARC Meeting

We are considering moving the CARC meeting on Glyphosate from June 24th to July 8th. Please let me know ASAP if you CANNOT make the July 8th meeting date.

Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; OPP HED CARC[OPP_HED_CARC@epa.gov]; Christensen, Carol[Christensen.Carol@epa.gov]; Sarkar, Bayazid[Sarkar.Bayazid@epa.gov]; Shah, Aruna[Shah.Aruna@epa.gov]; Tao, Jenny[Tao.Jenny@epa.gov]; Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Miller, David[Miller.DavidJ@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]
Cc: Kidwell, Jessica[kidwell.jessica@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Shah, Pv[Shah.Pv@epa.gov]
From: Liccione, John
Sent: Tue 5/26/2015 1:52:30 PM
Subject: RE: Glyphosate CARC Meeting

July 8th works good for me too… **Ex. 6 - Personal Privacy**
Ex. 6 - Personal Privacy

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
Subject: Glyphosate CARC Meeting

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Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; OPP HED CARC[OPP_HED_CARC@epa.gov]; Christensen, Carol[Christensen.Carol@epa.gov]; Sarkar, Bayazid[Sarkar.Bayazid@epa.gov]; Shah, Aruna[Shah.Aruna@epa.gov]; Tao, Jenny[Tao.Jenny@epa.gov]; Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Miller, David[Miller.DavidJ@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]
Cc: Kidwell, Jessica[kidwell.jessica@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Shah, Pv[Shah.Pv@epa.gov]
From: Middleton, Karlyn
Sent: Tue 5/26/2015 1:42:44 PM
Subject: RE: Glyphosate CARC Meeting

The 8th is good for me.

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
Subject: Glyphosate CARC Meeting

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Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Lobdell, Danelle
Sent: Tue 5/26/2015 1:32:15 PM
Subject: RE: Glyphosate CARC Meeting

July 8th works for me.

Danelle T. Lobdell, Ph.D., M.S.

Epidemiologist

National Health and Environmental Effects Research Laboratory

Environmental Public Health Division

Mail:

USEPA

MD 58A

Research Triangle Park, NC 27711

Package Delivery:

USEPA Human Studies Facility

104 Mason Farm Rd, Room 52

Chapel Hill, NC 27514-4512

Phone: 919-843-4434 Fax: 919-966-7584

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
Subject: Glyphosate CARC Meeting

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Thanks!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: McCarroll, Nancy
Sent: Tue 5/26/2015 1:31:49 PM
Subject: RE: Glyphosate CARC Meeting

Okay with me!

From: Brunsman, Lori
Sent: Tuesday, May 26, 2015 9:25 AM
To: OPP HED CARC; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; Schlosser, Christopher; Miller, David; Lobdell, Danelle; Wood, Charles
Cc: Kidwell, Jessica; Kent, Ray; Liccione, John; Middleton, Karlyn; Rowland, Jess; McCarroll, Nancy; Akerman, Gregory; Smith, Charles; Dunbar, Anwar; Shah, Pv
Subject: Glyphosate CARC Meeting

We are considering moving the CARC meeting on Glyphosate from June 24th to July 8th. Please let me know ASAP if you CANNOT make the July 8th meeting date.

Thanks!

Have a great day!

Lori

****

__Lori Brunsman, Statistician and Project Officer__
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Schlosser, Christopher[Schlosser.Christopher@epa.gov]
From: Dunbar, Anwar
Sent: Fri 5/8/2015 12:22:07 PM
Subject: Re: updated CARC schedule

Okay thanks Lori.

From: Brunsman, Lori
Sent: Wednesday, May 6, 2015 2:02 PM
To: Schlosser, Christopher; Dunbar, Anwar
Subject: updated CARC schedule

Anwar –

I just updated the CARC schedule and added Glyphosate due dates.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

To: Wade, Tim[Wade.Tim@epa.gov]
Cc: Rowland, Jess[Rowland.Jess@epa.gov]; Vogel, Dana[Vogel.Dana@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Cascio, Wayne[Cascio.Wayne@epa.gov]; Christensen, Carol[Christensen.Carol@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Miller, David
Sent: Wed 5/6/2015 6:32:53 PM
Subject: RE: Glyphosate Cancer Peer Review

Thanks !

She should have an invite on CaLANder from Lori Brunsman with details. We will be sure that a call –in number and other information is provided, closer to the date.

David.

From: Wade, Tim
Sent: Wednesday, May 06, 2015 2:28 PM
To: Miller, David
Cc: Rowland, Jess; Vogel, Dana; Lobdell, Danelle; Cascio, Wayne
Subject: Re: Glyphosate Cancer Peer Review

All- I apologize for the delay- I fully support Danelle's participation -thank- you. Tim

On May 6, 2015, at 2:25 PM, Miller, David <Miller.DavidJ@epa.gov> wrote:

Hello Tim,

I am just following up on Jess Rowland's note to you below. If this is something that Dr. Lobdell could participate in, we would greatly appreciate it.

Dr. Lobdell would not be expected to necessarily generate anything *de novo* for the meeting

– just review the briefing package and provide input during the meeting with respect to experience and thoughts.

Thanks.

David.

David J. Miller CAPT | USPHS

Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
703-305-5352 (voice)
703-305-5147 (fax)

Visit www.epa.gov/pesticides

From: Rowland, Jess
Sent: Thursday, April 30, 2015 2:31 PM
To: Wade, Tim
Cc: Vogel, Dana; Lobdell, Danelle
Subject: Glyphosate Cancer Peer Review
Importance: High

Hi Tim

The Cancer Assessment Review Peer Review Committee (CARC) of the Health Effects Division is scheduled to review the carcinogenic potential of Glyphosate on June 24th. This process entails a comprehensive review of data of animal carcinogenicity studies, mutagenicity, SAR, and other relevant information. We are planning to include the epidemiology data also in this evaluation. Therefore we would very much like Dr. Lobdell's participation at this meeting to provide her expertise in epidemiology. Dr. Charles Wood is our consulting pathologists and he participates in the CARC meetings. We will be sending them a "briefing package" on 10th. Charles routinely participates via teleconference. If this is OK with you, Dr. Lobdell can also follow suit.

We very much appreciate you help in this

Regards

Jess Rowland,

Deputy Director
Health Effects Division

Office of Pesticide Programs
703-308-2719

To: Miller, David[Miller.DavidJ@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]
Cc: Schlosser, Christopher[Schlosser.Christopher@epa.gov]
From: Christensen, Carol
Sent: Wed 5/6/2015 5:24:56 PM
Subject: Re: Glyphosate CARC Meeting

Yes, Danelle has been invited and I believe she accepted (I am not the meeting convener). I asked Jess R. to contact Danelle's Branch Chief Tim Wade to request her time as a consultant to this meeting.

Jess, have you contacted Tim Wade yet?

Carol

From: Miller, David
Sent: Wednesday, May 6, 2015 1:06 PM
To: Brunsman, Lori; Rowland, Jess; Christensen, Carol
Cc: Schlosser, Christopher
Subject: RE: Glyphosate CARC Meeting

Lori -- Has Daniell Lobdell responded to your invite to the June Glyphosate CARC meeting?

Carol – have you communicated with Danielle on this directly?

David.

From: Brunsman, Lori
Sent: Wednesday, April 29, 2015 7:32 AM
To: Rowland, Jess; Christensen, Carol; Miller, David
Cc: Schlosser, Christopher
Subject: RE: Glyphosate CARC Meeting

I have invited Danelle Lobdell to the Glyphosate CARC meeting.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer

Science Information Management Branch
Health Effects Division
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency
One Potomac Yard S-10934
brunsman.lori@epa.gov
703-308-2902

From: Rowland, Jess
Sent: Wednesday, April 29, 2015 7:11 AM
To: Christensen, Carol; Miller, David
Cc: Schlosser, Christopher; Brunsman, Lori
Subject: RE: Glyphosate CARC Meeting

Hi Carol

Ex. 5 - Deliberative Process

Regards
JR
Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

-----Original Appointment-----
From: Christensen, Carol **On Behalf Of** Brunsman, Lori
Sent: Tuesday, April 28, 2015 11:27 AM

To: Rowland, Jess; Miller, David; Smith, Charles
Subject: FW: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 10:30 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10100/Potomac-Yard-One

Ex. 5 - Deliberative Process

Thanks,

Carol

-----Original Appointment-----
From: Brunsman, Lori
Sent: Tuesday, April 28, 2015 8:51 AM
To: Brunsman, Lori; Schlosser, Christopher; Miller, David; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; OPP HED CARC
Cc: Kidwell, Jessica
Subject: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 10:30 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10100/Potomac-Yard-One

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; Christensen, Carol[Christensen.Carol@epa.gov]
Cc: Schlosser, Christopher[Schlosser.Christopher@epa.gov]
From: Miller, David
Sent: Wed 5/6/2015 5:06:32 PM
Subject: RE: Glyphosate CARC Meeting

Lori -- Has Daniell Lobdell responded to your invite to the June Glyphosate CARC meeting?

Carol - have you communicated with Danielle on this directly?

David.

From: Brunsman, Lori
Sent: Wednesday, April 29, 2015 7:32 AM
To: Rowland, Jess; Christensen, Carol; Miller, David
Cc: Schlosser, Christopher
Subject: RE: Glyphosate CARC Meeting

I have invited Danelle Lobdell to the Glyphosate CARC meeting.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency
One Potomac Yard S-10934
brunsman.lori@epa.gov
703-308-2902

From: Rowland, Jess
Sent: Wednesday, April 29, 2015 7:11 AM
To: Christensen, Carol; Miller, David
Cc: Schlosser, Christopher; Brunsman, Lori
Subject: RE: Glyphosate CARC Meeting

Hi Carol

Ex. 5 - Deliberative Process

Regards
JR
Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

-----Original Appointment-----
From: Christensen, Carol **On Behalf Of** Brunsman, Lori
Sent: Tuesday, April 28, 2015 11:27 AM
To: Rowland, Jess; Miller, David; Smith, Charles
Subject: FW: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 10:30 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
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Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Thanks,

Carol

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Sent: Tuesday, April 28, 2015 8:51 AM
To: Brunsman, Lori; Schlosser, Christopher; Miller, David; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; OPP HED CARC
Cc: Kidwell, Jessica
Subject: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 10:30 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10100/Potomac-Yard-One

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Rowland, Jess
Sent: Wed 5/6/2015 3:06:28 PM
Subject: RE: Glyphosate Male Mouse Updated Tumor Counts

LB

Thank you very much. Yes, please make your standard table for inclusion into the CARC document and send it to me

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Brunsman, Lori
Sent: Wednesday, May 06, 2015 11:05 AM
To: Rowland, Jess
Subject: Glyphosate Male Mouse Updated Tumor Counts

Jess –

Ex. 5 - Deliberative Process

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

From: Shah, Pv
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

To: Rowland, Jess[Rowland.Jess@epa.gov]; Miller, David[Miller.DavidJ@epa.gov]
Cc: Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Christensen, Carol
Sent: Wed 4/29/2015 1:10:57 PM
Subject: RE: Glyphosate CARC Meeting

Hi

Sounds like a great plan. I will have the materials prepared by June 10th.

Thanks

Carol

From: Rowland, Jess
Sent: Wednesday, April 29, 2015 7:11 AM
To: Christensen, Carol; Miller, David
Cc: Schlosser, Christopher; Brunsman, Lori
Subject: RE: Glyphosate CARC Meeting

Hi Carol

Ex. 5 - Deliberative Process

Regards
JR
Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

-----Original Appointment-----
From: Christensen, Carol **On Behalf Of** Brunsman, Lori
Sent: Tuesday, April 28, 2015 11:27 AM
To: Rowland, Jess; Miller, David; Smith, Charles
Subject: FW: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 10:30 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10100/Potomac-Yard-One

Ex. 5 - Deliberative Process

Thanks,

Carol

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From: Brunsman, Lori
Sent: Tuesday, April 28, 2015 8:51 AM
To: Brunsman, Lori; Schlosser, Christopher; Miller, David; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; OPP HED CARC
Cc: Kidwell, Jessica
Subject: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 10:30 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10100/Potomac-Yard-One

To: Christensen, Carol[Christensen.Carol@epa.gov]; Miller, David[Miller.DavidJ@epa.gov]
Cc: Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Rowland, Jess
Sent: Wed 4/29/2015 11:10:43 AM
Subject: RE: Glyphosate CARC Meeting

Hi Carol

Ex. 5 - Deliberative Process

Regards
JR
Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

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From: Christensen, Carol **On Behalf Of** Brunsman, Lori
Sent: Tuesday, April 28, 2015 11:27 AM
To: Rowland, Jess; Miller, David; Smith, Charles
Subject: FW: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 10:30 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10100/Potomac-Yard-One

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Thanks,

Carol

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From: Brunsman, Lori
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To: Brunsman, Lori; Schlosser, Christopher; Miller, David; Christensen, Carol; Sarkar, Bayazid; Shah, Aruna; Tao, Jenny; OPP HED CARC
Cc: Kidwell, Jessica
Subject: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 10:30 AM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS10100/Potomac-Yard-One

From: Dunbar, Anwar
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Christensen, Carol
Sent: Tue 4/28/2015 5:30:47 PM
Subject: RE: Meeting Forward Notification: Glyphosate CARC Meeting

Ex. 5 - Deliberative Process

From: Brunsman, Lori
Sent: Tuesday, April 28, 2015 12:21 PM
To: Christensen, Carol
Subject: RE: Meeting Forward Notification: Glyphosate CARC Meeting

Carol -

In case you didn't know, Jess is co-chair of the CARC. He is automatically invited to every CARC meeting.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency
One Potomac Yard S-10934
brunsman.lori@epa.gov
703-308-2902

-----Original Appointment-----
From: Microsoft Outlook **On Behalf Of** Christensen, Carol
Sent: Tuesday, April 28, 2015 11:27 AM
To: Brunsman, Lori
Subject: Meeting Forward Notification: Glyphosate CARC Meeting
When: Wednesday, June 24, 2015 2:30 PM-4:30 PM (UTC) Monrovia, Reykjavik.
Where: DCRoomPYS10100/Potomac-Yard-One

Your meeting was forwarded

Christensen, Carol has forwarded your meeting request to additional recipients.

Meeting
Glyphosate CARC Meeting

Meeting Time
Wednesday, June 24, 2015 10:30 AM-12:30 PM.

Recipients
Rowland, Jess
Miller, David
Smith, Charles

All times listed are in the following time zone: (UTC-05:00) Eastern Time (US & Canada)

From: Microsoft Outlook
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Meeting Forward Notification: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

Your meeting was forwarded

Christensen, Carol has forwarded your meeting request to additional recipients.

Meeting
Glyphosate CARC Meeting

Meeting Time
Wednesday, June 24, 2015 10:30 AM-12:30 PM.

Recipients
Rowland, Jess
Miller, David
Smith, Charles

All times listed are in the following time zone: (UTC-05:00) Eastern Time (US & Canada)

Sent by Microsoft Exchange Server 2016

From: McCarroll, Nancy
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

From: Christensen, Carol
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

From: Rowland, Jess
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

From: Middleton, Karlyn
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

From: Miller, David
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

From: Liccione, John
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Declined: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

I will be in jellystone

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: May, Brenda
Sent: Tue 4/28/2015 12:56:46 PM
Subject: Just curious....

Who (which toxicologist) is bringing Glyphosate to the CARC?

Brenda May, Chief
Science Information Management Branch and

Information Management and Contract Support Branch (Acting)
Health Effects Division (Mail Code 7509P)
Office of Pesticide Programs US EPA
(703) 308-6175
may.brenda@epa.gov

From: Kent, Ray
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

From: Wood, Charles
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

From: Kidwell, Jessica
Location: DCRoomPYS10100/Potomac-Yard-One
Importance: Normal
Subject: Accepted: Glyphosate CARC Meeting
Start Date/Time: Wed 6/24/2015 2:30:00 PM
End Date/Time: Wed 6/24/2015 4:30:00 PM

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
Cc: Brooks, Larry[Brooks.Larry@epa.gov]
From: May, Brenda
Sent: Wed 9/16/2015 7:27:08 PM
Subject: RE: Glyphosate in ISTEP?

Let's wait for the final report.

Thanks.

Brenda May, Chief
Science Information Management Branch and

Information Management and Contract Support Branch (Acting)
Health Effects Division (Mail Code 7509P)
Office of Pesticide Programs US EPA
(703) 308-6175
may.brenda@epa.gov

From: Brunsman, Lori
Sent: Wednesday, September 16, 2015 3:26 PM
To: May, Brenda
Cc: Brooks, Larry
Subject: Glyphosate in ISTEP?

Brenda –

Ex. 5 - Deliberative Process

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Rowland, Jess
Sent: Thur 9/17/2015 5:56:06 PM
Subject: RE: Glyphosate

Thanks.

Ex. 5 - Deliberative Process

BTW, did we run out $ for the chemistry contract. Someone, think, Thurgood, asked if we have $ to send chemistry work

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Brunsman, Lori
Sent: Thursday, September 17, 2015 1:39 PM
To: Rowland, Jess
Subject: RE: Glyphosate

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Rowland, Jess
Sent: Thursday, September 17, 2015 1:18 PM
To: Brunsman, Lori
Subject: RE: Glyphosate

LB

Great thanks.

What happened at the contractgs meeting. Send me a summary/bottom line please

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Brunsman, Lori
Sent: Thursday, September 17, 2015 1:13 PM
To: Rowland, Jess
Subject: RE: Glyphosate

By the way, the denominators are 49, 49, 50, and 50, for the control, 1000, 5000 and 30,000 ppm dose groups, respectively.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Rowland, Jess
Sent: Thursday, September 17, 2015 10:35 AM
To: Brunsman, Lori
Subject: Glyphosate
Importance: High

HI LB

This excerpt is from the PWG report (TXR No. 005590). Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Thanks

"The incidence of renal tubular-cell neoplasms as determined by the PWG is presented in Table I. Because differentiation between tubular-cell adenoma and tubular-cell carcinoma is not always clearly apparent and because both lesions are derived from the same cell type it is appropriate to combine the incidences

for purposes of evaluation and statistical analysis."

Table. Male Mouse Renal Tumors in the 1983 Mouse Study

	Control	1000 ppm	5000 ppm	30,000 ppm
Tubular cell adenoma	1	0	0	1
Tubular cell carcinoma	0	0	1	2
Combined incidence	1	0	1	3

This PWG firmly believes and unanimously· concurs with the original pathologist and reviewing pathologist that the incidences of renal tubular-cell neoplasms in this study are not compound related."

None of the treatment groups differed from the controls by the Fisher exact test at the 0.05 level of significance. Over all groups there was no evidence of a significant linear trend at the 0.05 level by a one-tailed Cochran-Armitage Test."

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Rowland, Jess
Sent: Thur 9/17/2015 5:18:06 PM
Subject: RE: Glyphosate

LB

Great thanks.

What happened at the contractgs meeting. Send me a summary/bottom line please

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Brunsman, Lori
Sent: Thursday, September 17, 2015 1:13 PM
To: Rowland, Jess
Subject: RE: Glyphosate

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Have a great day!

Lori

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Lori Brunsman, Statistician and Project Officer
Science Information Management Branch

Health Effects Division
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One Potomac Yard S-10934

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Ex. 5 - Deliberative Process

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Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Brunsman, Lori[Brunsman.Lori@epa.gov]
From: Rowland, Jess
Sent: Thur 9/17/2015 6:06:57 PM
Subject: RE: Glyphosate

What I was asking,…if there $ in the chem contract at present to send work

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Brunsman, Lori
Sent: Thursday, September 17, 2015 2:05 PM
To: Rowland, Jess
Subject: RE: Glyphosate

I have no idea about money for chemistry work. There were no specific contracts talked about in the main meeting, just Tammy and I talked after everybody else left.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Rowland, Jess
Sent: Thursday, September 17, 2015 1:56 PM
To: Brunsman, Lori
Subject: RE: Glyphosate

Thanks.

Ex. 5 - Deliberative Process

BTW, did we run out $ for the chemistry contract. Someone, think, Thurgood, asked if we have $ to send chemistry work

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Brunsman, Lori
Sent: Thursday, September 17, 2015 1:39 PM
To: Rowland, Jess
Subject: RE: Glyphosate

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
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Subject: RE: Glyphosate

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Deputy Director
Health Effects Division
703-308-2719

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Have a great day!

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Subject: Glyphosate
Importance: High

HI LB

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Ex. 5 - Deliberative Process

Thanks

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JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: May, Brenda[May.Brenda@epa.gov]
From: Brunsman, Lori
Sent: Tue 9/29/2015 11:29:10 AM
Subject: RE: Glyphosate in ISTEP?

Brenda -

Ex. 5 - Deliberative Process

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: May, Brenda
Sent: Wednesday, September 16, 2015 3:27 PM
To: Brunsman, Lori
Cc: Brooks, Larry
Subject: RE: Glyphosate in ISTEP?

Let's wait for the final report.

Thanks.

Brenda May, Chief
Science Information Management Branch and

Information Management and Contract Support Branch (Acting)
Health Effects Division (Mail Code 7509P)
Office of Pesticide Programs US EPA
(703) 308-6175
may.brenda@epa.gov

From: Brunsman, Lori
Sent: Wednesday, September 16, 2015 3:26 PM
To: May, Brenda
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Subject: Glyphosate in ISTEP?

Brenda –

Ex. 5 - Deliberative Process

Have a great day!

Lori

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Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
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Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov

703-308-2902

“When you have more than you need, build a longer table, not a higher fence.”

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Brunsman, Lori
Sent: Mon 9/28/2015 3:29:36 PM
Subject: Re: Glyphosate

Jess -

Ex. 5 - Deliberative Process

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency
One Potomac Yard S-10934
brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Rowland, Jess
Sent: Sunday, September 27, 2015 9:02 PM
To: Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kent, Ray; Liccione, John; Lobdell, Danelle; Middleton, Karlyn; McCarroll, Nancy; Wood, Charles
Subject: Glyphosate

Greg et al.,

Ex. 5 - Deliberative Process

Thanks to Greg, we have made all the necessary revisions.

Ex. 5 - Deliberative Process

Thanks for all your help; special thanks to the valuable contributions by Charles and Danelle.

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Lobdell, Danelle[Lobdell.Danelle@epa.gov]
From: Brunsman, Lori
Sent: Wed 9/23/2015 5:42:00 PM
Subject: RE: Glyphosate- Classification Narrative

Thanks for the clarification, Danelle!

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Lobdell, Danelle
Sent: Monday, September 21, 2015 2:58 PM
To: Brunsman, Lori; Wood, Charles; Rowland, Jess; OPP HED CARC
Subject: RE: Glyphosate- Classification Narrative

They recently have changed the name of Hodgkin's lymphoma to Hodgkin Lymphoma… taking out the apostrophe s. See: http://www.cancer.gov/types/lymphoma

Danelle T. Lobdell, Ph.D., M.S.

Epidemiologist

National Health and Environmental Effects Research Laboratory

Environmental Public Health Division

Mail:

USEPA

MD 58A

Research Triangle Park, NC 27711

Package Delivery:

USEPA Human Studies Facility

104 Mason Farm Rd, Room 52

Chapel Hill, NC 27514-4512

Phone: 919-843-4434 Fax: 919-966-7584

From: Brunsman, Lori
Sent: Monday, September 21, 2015 2:24 PM
To: Wood, Charles; Rowland, Jess; OPP HED CARC; Lobdell, Danelle
Subject: Re: Glyphosate- Classification Narrative

I agree with Charles, although I think "Hodgkin" lymphoma should be "Hodgkin's" with an apostrophe "s".

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency

One Potomac Yard S-10934
brunsman.lori@epa.gov
703-308-2902
"When you have more than you need, build a longer table, not a higher fence."

From: Wood, Charles
Sent: Monday, September 21, 2015 1:58 PM
To: Rowland, Jess; OPP HED CARC; Lobdell, Danelle
Subject: RE: Glyphosate- Classification Narrative

Jess et al,

See edits/suggestions below in red. I borrowed several changes from others.

--Charles

From: Rowland, Jess
Sent: Monday, September 21, 2015 12:24 PM
To: OPP HED CARC; Lobdell, Danelle
Subject: Glyphosate- Classification Narrative
Importance: High

Hello CARCeers

Here is the narrative that will go into the CARC document.

I want to get this out for your comments since this "blurb" has to go into the risk assessment document which is due before the Pope get it !!!

So, u know what that means…..I need your comments by COB. It is not long…so u should make it !!

Thanks

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

Ex. 5 - Deliberative Process

To: Dave Brunsman[Ex. 6 - Personal Privacy]
From: Brunsman, Lori
Sent: Wed 9/23/2015 5:12:35 PM
Subject: you know it's bad when .....

You know it's bad when your division director refers to the Share"-pointless" site's failure to "share" as "This is turning into a CF." (see below)

Hoping your day is going well!

Love, Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Rowland, Jess
Sent: Wednesday, September 23, 2015 12:18 PM
To: Akerman, Gregory; Brunsman, Lori; Kent, Ray; McCarroll, Nancy; Middleton, Karlyn; May, Brenda; Dunbar, Anwar; Akerman, Gregory; Powell, Calvin
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Ok. This is turning into a CF.
Lori u have rights to CARC discussion db.
Please post CPRs version.
Every one make your edits in track changes. I am in Friday. I will collate and revise the documents.
Lori if you don't have rights, Jessica you post it

Sent from my Windows Phone

From: Akerman, Gregory
Sent: 9/23/2015 12:03 PM
To: Rowland, Jess
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Maybe Jessica should just post the version that Cal formated (he already sent it to her) and we can make edits using track changes as we normally do. I will help pull all the edits together tomorrow.

From: Rowland, Jess
Sent: Wednesday, September 23, 2015 11:51 AM
To: Brunsman, Lori; Kidwell, Jessica; Middleton, Karlyn; Akerman, Gregory; Lobdell, Danelle; Chen, Jonathan; Liccione, John; Wood, Charles; Dunbar, Anwar; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

At home it should be called share pointless . Another crown · of OEI

Sent from my Windows Phone

From: Brunsman, Lori
Sent: 9/23/2015 11:48 AM
To: Kidwell, Jessica; Middleton, Karlyn; Akerman, Gregory; Lobdell, Danelle; Chen, Jonathan; Liccione, John; Wood, Charles; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

I think the problem must have to do with accessing Sharepoint from home. It works fine here at the office.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:48 AM
To: Middleton, Karlyn; Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Maybe there's some code in there preventing us from editing. I don't know.

From: Middleton, Karlyn
Sent: Wednesday, September 23, 2015 11:47 AM
To: Kidwell, Jessica; Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Not working.

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:46 AM
To: Kidwell, Jessica; Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Middleton, Karlyn; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

This still doesn't work for me. Does it work for anyone else? If it's not working I'm going to take it down. Please let me know.

From: Kidwell, Jessica

Sent: Wednesday, September 23, 2015 11:43 AM
To: Akerman, Gregory; Lobdell, Danelle; Brunsman, Lori; Chen, Jonathan; Liccione, John; Wood, Charles; Middleton, Karlyn; Dunbar, Anwar; Rowland, Jess; Kent, Ray; McCarroll, Nancy
Cc: Kidwell, Jessica
Subject: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Let's see if we're able to edit this version. This is Jess's file which has Cal's formatting edits. Please share this with anyone I missed on CARC.

Open Glyphosate CARC Final 9.21.15_cpr_JMK.docx

Followthis document to get updates in your newsfeed.

To: Kidwell, Jessica[kidwell.jessica@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; Akerman, Gregory[Akerman.Gregory@epa.gov]; Lobdell, Danelle[Lobdell.Danelle@epa.gov]; Chen, Jonathan[Chen.Jonathan@epa.gov]; Liccione, John[Liccione.John@epa.gov]; Wood, Charles[Wood.Charles@epa.gov]; Dunbar, Anwar[Dunbar.Anwar@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; Kent, Ray[Kent.Ray@epa.gov]; McCarroll, Nancy[McCarroll.Nancy@epa.gov]
From: Brunsman, Lori
Sent: Wed 9/23/2015 3:48:27 PM
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

I think the problem must have to do with accessing Sharepoint from home. It works fine here at the office.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

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Followthis document to get updates in your newsfeed.

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From: Brunsman, Lori
Sent: Wed 9/23/2015 3:47:36 PM
Subject: RE: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

It works for me here at the office.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

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Environmental Protection Agency
One Potomac Yard S-10934

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703-308-2902

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Cc: Kidwell, Jessica
Subject: Kidwell, Jessica has shared 'Glyphosate CARC Final 9.21.15_cpr_JMK'

Let's see if we're able to edit this version. This is Jess's file which has Cal's formatting edits. Please share this with anyone I missed on CARC.

Open Glyphosate CARC Final 9.21.15_cpr_JMK.docx

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To: Kidwell, Jessica[kidwell.jessica@epa.gov]
From: Brunsman, Lori
Sent: Wed 9/23/2015 3:17:57 PM
Subject: RE: please do QA ASAP

Thanks! I don't think it'll take too long.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:17 AM
To: Brunsman, Lori
Subject: RE: please do QA ASAP

I'll do it right now.

From: Brunsman, Lori
Sent: Wednesday, September 23, 2015 11:16 AM
To: Kidwell, Jessica
Subject: please do QA ASAP

Jessica –

Jess asked me to write up a qual memo on the Glyphosate ad hoc stats I did for the CARC meeting.

My memo and the ad hoc analyses I did are attached. All of the DERs were in the CARC package (except for the Nufarm 2009 study; there is no DER, just cited in Greims et al 2015).

Jess would like it out today. Any chance you can do that? I'm only here today until 2:00.

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

To: Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]; Miller, David[Miller.DavidJ@epa.gov]; Smith, Charles[Smith.Charles@epa.gov]
Cc: Lobdell, Danelle[Lobdell.Danelle@epa.gov]
From: Christensen, Carol
Sent: Tue 5/26/2015 5:37:19 PM
Subject: Glyphosate Cancer Epi CARC materials

Hi –

Please find glyphosate cancer epi CARC materials at: G:\Epidemiology Files_May2015\Glyphosate Epi for CARC. PDFs are included.

I have shared these materials with Dr. Lobdell, NHERRL.

Thanks and best of luck.

Carol

To: Cyran, Carissa[Cyran.Carissa@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Mon 2/23/2015 5:03:54 PM
Subject: IARC, Glyphosate and Carcinogenicity
GLY IARC Short List.docx

Carissa:

Just following up from our conversation this morning: I think the EPA participants at IARC are Peter P. Egeghy & Matthew T. Martin (believe they are at ORD in North Carolina) and EPA observers are Catherine Eiden & Jess Rowland. We just wanted to share a short list of published literature as not all the folks from EPA might be familiar with these citations or EPA's recent conclusions.

Thanks for passing along,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

1. **Greim, H., D. Saltmiras, V. Mostert, and C. Strupp. 2015. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Crit.* Rev. Toxicol. In press**

    Summary: A new scientific publication examining 14 separate cancer studies in rats and mice conducted over the last several decades concludes that there is no evidence that glyphosate, the active ingredient in Roundup branded herbicides, causes cancer. The article,in Critical Reviews in Toxicology, evaluated the data from these long term studies to determine whether there were any patterns to suggest humans exposed to glyphosate would have any concern about developing cancer. Other scientifically relevant information such as expert regulator evaluations, human dietary exposures and epidemiological studies were also discussed. The clear and consistent view across over 30 years of relevant information continues to support the first expert opinions from the 1980's, that glyphosate does not cause cancer.

    Abstract: Glyphosate, an herbicidal derivative of the amino acid glycine, was introduced to agriculture in the 1970s. Glyphosate targets and blocks a plant metabolic pathway not found in animals, the shikimate pathway, required for the synthesis of aromatic amino acids in plants. After almost forty years of commercial use, and multiple regulatory approvals including toxicology evaluations, literature reviews, and numerous human health risk assessments, the clear and consistent conclusions are that glyphosate is of low toxicological concern, and no concerns exist with respect to glyphosate use and cancer in humans. This manuscript discusses the basis for these conclusions. Most toxicological studies informing regulatory evaluations are of commercial interest and are proprietary in nature. Given the widespread attention to this molecule, the authors gained access to carcinogenicity data submitted to regulatory agencies and present overviews of each study, followed by a weight of evidence evaluation of tumor incidence data. Fourteen carcinogenicity studies (nine rat and five mouse) are evaluated for their individual reliability, and select neoplasms are identified for further evaluation across the data base. The original tumor incidence data from study reports are presented in the online data supplement. There was no evidence of a carcinogenic effect related to glyphosate treatment. The lack of a plausible mechanism, along with published epidemiology studies, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans.

2. **EPA**

    2009 EPA Glyphosate Reg Review
    Carcinogenicity was not identified as a concern in the work plan
    http://www.epa.gov/oppsrrd1/registration_review/glyphosate/

    2013 Federal Register Notice (FR 25396 Vol. 78, No. 84, Wednesday, May 1, 2013) Final Rule new tolerances in or on multiple commodities: "EPA has concluded that glyphosate does not pose a cancer risk to humans."
    http://www.gpo.gov/fdsys/pkg/FR-2013-05-01/pdf/2013-10316.pdf

3. **Sorahan, T. (2015). Multiple Myeloma and Glyphosate Use: A Re-Analysis of US Agricultural Health Study (AHS) Data. *Int. J. Environ. Res. Public Health***
http://www.ncbi.nlm.nih.gov/pubmed/25635915

Summary: A new look at data from the US Agricultural Health Study (AHS) clarifies that there is no relationship between glyphosate use and the risk of multiple myeloma, a type of cancer. The study considered data collected from over 57,000 pesticide applicators to determine whether a relationship exists between multiple myeloma and glyphosate exposure. These results contradict the outcome of a previous analysis of AHS data that relied on a restricted data set to reach a different conclusion. This reanalysis of the full AHS data set for multiple myeloma is consistent with other epidemiological and laboratory research that demonstrated glyphosate does not cause cancer.

Abstract: A previous publication of 57,311 pesticide applicators enrolled in the US Agricultural Health Study (AHS) produced disparate findings in relation to multiple myeloma risks in the period 1993-2001 and ever-use of glyphosate (32 cases of multiple myeloma in the full dataset of 54,315 applicators without adjustment for other variables: rate ratio (RR) 1.1, 95% confidence interval (CI) 0.5 to 2.4; 22 cases of multiple myeloma in restricted dataset of 40,719 applicators with adjustment for other variables: RR 2.6, 95% CI 0.7 to 9.4). It seemed important to determine which result should be preferred. RRs for exposed and non-exposed subjects were calculated using Poisson regression; subjects with missing data were not excluded from the main analyses. Using the full dataset adjusted for age and gender the analysis produced a RR of 1.12 (95% CI 0.50 to 2.49) for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of ten other pesticides had little effect (RR 1.24, 95% CI 0.52 to 2.94). There were no statistically significant trends for multiple myeloma risks in relation to reported cumulative days (or intensity weighted days) of glyphosate use. The doubling of risk reported previously arose from the use of an unrepresentative restricted dataset and analyses of the full dataset provides no convincing evidence in the AHS for a link between multiple myeloma risk and glyphosate use.

4. **Kier, L. D. (2015). Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations. Crit. Rev. Toxicol., in press**

Summary: A recent review examined several studies that allege damage to the DNA in cells collected from people after self-reported exposures to glyphosate-based herbicides. The author concluded that there are no direct risks to human DNA under normal exposure conditions. These findings are consistent with an earlier review of an extensive number of laboratory studies that also demonstrated no direct effect on DNA. Taken together, these results confirm previous conclusions that glyphosate-based herbicides do not damage DNA in humans following real world exposures.

Abstract: Human and environmental genotoxicity biomonitoring studies involving exposure to glyphosate - based formulations (GBFs) were reviewed to complement an earlier review of experimental genotoxicity studies of glyphosate and GBF's (Kier and Kirkland, 2013). The environmental and many of the human biomonitoring studies were not informative because there was either a very low frequency of GBF exposure or exposure to a large number of pesticides. One human biomonitoring study indicated no statistically significant correlation between frequency of GBF exposure reported for the last spraying season and oxidative DNA damage. Negative results for the lymphocyte cytokinesis - block micronucleus (CBMN) endpoint were observed in a second human monitoring study with exposure to several pesticides including GBF. There were three studies of human populations exposed to GBF aerial spraying. One study found increases for the CBMN endpoint but these increases did not correlate with self - reported spray exposure or application rates. A second study found increases for the blood cell comet endpoint at high exposures causing toxicity. However, a follow - up to this study two years after spraying did not indicate chromosomal effects. The results of the biomonitoring studies do not contradict an earlier conclusion derived from experimental genotoxicity studies that typical GBF's do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

5. **Kier, LD and DJ. Kirkland. 2013. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Critical Reviews in Toxicology. 43:283.**
http://www.ncbi.nlm.nih.gov/pubmed/23480780

Summary: A review of an extensive number of laboratory studies examining the potential for glyphosate and glyphosate-based herbicides to damage DNA concludes that these products do not damage DNA under normal exposure conditions. This review includes peer-reviewed publications and regulatory studies. The evaluation of the large amount of data available confirms that glyphosate is not genotoxic to humans and that glyphosate and glyphosate-based products do not damage DNA under normal exposures.

Abstract: An earlier review of the toxicity of glyphosate and the original Roundup™-branded formulation concluded that neither glyphosate nor the formulation poses a risk for the production of heritable/somatic mutations in humans. The present review of subsequent genotoxicity publications and regulatory studies of glyphosate and glyphosate-based formulations (GBFs) incorporates all of the findings into a weight of evidence for genotoxicity. An overwhelming preponderance of negative results in well-conducted bacterial reversion and in vivo mammalian micronucleus and chromosomal aberration assays indicates that glyphosate and typical GBFs are not genotoxic in these core assays. Negative results for in vitro gene mutation and a majority of negative results for chromosomal effect assays in mammalian cells add to the weight of evidence that glyphosate is not typically genotoxic for these endpoints in mammalian systems. Mixed results were observed for micronucleus assays of GBFs in non-mammalian systems. Reports of positive results for DNA damage endpoints indicate that glyphosate and GBFs tend to elicit DNA damage effects at high or toxic dose levels, but the data suggest that this is due to cytotoxicity rather than DNA interaction with GBF activity perhaps associated with the surfactants present in many GBFs. Glyphosate and typical GBFs do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

6. **Mink, P., J. Mandel, B. Sceurman, J. Lundin. 2012. Epidemiologic studies of glyphosate and cancer: A review. Regulatory Toxicology and Pharmacology. 63:3.**
http://www.sciencedirect.com/science/article/pii/S0273230012000943

Summary: A review of 21 epidemiological studies found no causal relationship between exposure to glyphosate and cancer in adults or children. This observation is consistent with conclusions from regulatory authorities that glyphosate is unlikely to pose a risk to human health based on previous toxicology studies.

Abstract: The United States Environmental Protection Agency and other regulatory agencies around the world have registered glyphosate as a broad-spectrum herbicide for use on multiple food and non-food use crops. Glyphosate is widely considered by regulatory authorities and scientific bodies to have no carcinogenic potential, based primarily on results of carcinogenicity studies of rats and mice. To examine potential cancer risks in humans, we reviewed the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans. We also reviewed relevant methodological and biomonitoring studies of glyphosate. Seven cohort studies and fourteen case-control studies examined the association between glyphosate and one or more cancer outcomes. Our review found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate. Data from biomonitoring studies underscore the importance of exposure assessment in epidemiologic studies, and indicate that studies should incorporate not only duration and frequency of pesticide use, but also type of pesticide formulation. Because generic exposure assessments likely lead to exposure misclassification, it is recommended that exposure algorithms be validated with biomonitoring data.

7. **Niemann, L., C. Sieke, R. Pfeil, R. Solecki. 2015. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. Journal of Consumer Protection and Food Safety.**
http://rd.springer.com/article/10.1007%2Fs00003-014-0927-3

Summary: The German Federal Institute for Risk Assessment reviewed seven existing biomonitoring studies where trace amounts of glyphosate were found in human urine samples. The authors concluded that at thelevels of glyphosate found, there is no concern for human health. After oral intake glyphosate is not metabolized significantly by humans and is rapidly excreted in urine. By measuring urine levels it is possible to calculate internal exposure levels. They concluded that realistic exposures are low and are well below the worst-case assumptions used by regulatory agencies.

Abstract: For active substances in plant protection products (PPP) with well defined urinary elimination, no potential for accumulation and virtually no metabolism, measuring of urine levels could be a powerful tool for human biomonitoring. Such data may provide reliable estimates of actual internal human exposure that can be compared to appropriate reference values, such as the 'acceptable daily intake (ADI)' or the 'acceptable operator exposure level (AOEL)'. Traces of the active compound glyphosate were found in human urine samples, probably resulting either from occupational use for plant protection purposes or from dietary intake of residues. A critical review and comparison of data obtained in a total of seven studies from Europe and the US was performed. The conclusion can be drawn that no health concern was revealed because the resulting exposure estimates were by magnitudes lower than the ADI or the AOEL. The expected internal exposure was clearly below the worst-case predictions made in the evaluation of glyphosate as performed for the renewal of its approval within the European Union. However, differences in the extent of exposure with regard to the predominant occupational and dietary exposure routes and between Europe and North America

became apparent.

To: 'JENKINS, DANIEL J [AG/1920]'[daniel.j.jenkins@monsanto.com]
From: Cyran, Carissa
Sent: Thur 4/9/2015 6:15:12 PM
Subject: RE: Desk Statement

Thank you.

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Thursday, April 09, 2015 1:46 PM
To: Cyran, Carissa
Subject: RE: Desk Statement

This is being couriered to you this afternoon

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Cyran, Carissa [mailto:Cyran.Carissa@epa.gov]
Sent: Tuesday, April 07, 2015 2:02 PM
To: JENKINS, DANIEL J [AG/1920]
Subject: RE: Desk Statement

Hello, Dan,

Thanks for the notification about the Korean government. Yes, can you please send the slides so I can share with everyone who participated at the meeting.

Thank you in advance.

Carissa

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Friday, April 03, 2015 4:27 PM
To: Cyran, Carissa
Subject: RE: Desk Statement

Carissa:

The Korean regulators (MFDS) will likely be sending you an email requesting EPA's view. Apparently they already sent one and haven't heard back.

Re: the presentation- I don't think we can redact it as we consider the method confidential still. do you still want the slides?

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Cyran, Carissa [mailto:Cyran.Carissa@epa.gov]
Sent: Thursday, April 02, 2015 12:57 PM
To: LISTELLO, JENNIFER J [AG/1000]
Cc: JENKINS, DANIEL J [AG/1920]
Subject: RE: Desk Statement

Hello, Jen,

The EPA has issued the following desk statement regarding IARC and glyphosate.

In 1991 EPA concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) based on a lack of convincing carcinogenicity evidence and considering the criteria in EPA Guidelines for classifying a carcinogen. Since then, EPA has monitored emerging research on the carcinogenicity of glyphosate.

In 2014, EPA reviewed over 55 epidemiological studies conducted on the possible cancer and non-cancer effects of glyphosate. Our review concluded that this body of research does not provide evidence to show that glyphosate causes cancer, and it does not warrant any change in EPA's cancer classification for glyphosate. This is the same conclusion reached in 2004 by the United Nations' Food and Agriculture Organization and affirmed this year by Germany's pesticide regulatory officials. In a few months, EPA will be releasing for public comment our preliminary human health risk assessment for glyphosate as part of our program to reevaluate all pesticides periodically. EPA is aware of the recent International Agency for Research on Cancer (IARC) report and will address it in detail in the preliminary risk assessment. Additional information regarding glyphosate and EPA's ongoing registration review can be found at: http://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:31:0::NO:1,3,31,7,12,25:P3_XCHEMICAL_II

Please let me know if you have any additional questions. Also, Dan, when you have the chance please send the redacted slides from the presentation on Monday.

Thank you,

Carissa

From: LISTELLO, JENNIFER J [AG/1000] [mailto:jennifer.j.listello@monsanto.com]
Sent: Thursday, April 02, 2015 12:23 PM
To: Cyran, Carissa
Cc: JENKINS, DANIEL J [AG/1920]
Subject: Desk Statement

Hi Carissa,

Thanks for a great discussion on Monday; please let us know if there is anything additional that you need.

I understand EPA has a desk statement regarding glyphosate/IARC. Can you please provide that statement?

Thanks,

Jen

This e-mail message may contain privileged and/or confidential information, and is intended to be received only by persons entitledto receive such information. If you have received this e-mail in error, please notify the sender immediately. Please delete it andall attachments from any servers, hard drives or any other media. Other use of this e-mail by you is strictly prohibited. All e-mails and attachments sent and received are subject to monitoring, reading and archival by Monsanto, including itssubsidiaries. The recipient of this e-mail is solely responsible for checking for the presence of "Viruses" or other "Malware".Monsanto, along with its subsidiaries, accepts no liability for any damage caused by any such code transmitted by or accompanyingthis e-mail or any attachment. The information contained in this email may be subject to the export control laws and regulations of the United States, potentiallyincluding but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department ofTreasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with allapplicable U.S. export laws and regulations.

To: 'JENKINS, DANIEL J [AG/1920]'[daniel.j.jenkins@monsanto.com]
From: Cyran, Carissa
Sent: Tue 4/7/2015 6:02:21 PM
Subject: RE: Desk Statement

Hello, Dan,

Thanks for the notification about the Korean government. Yes, can you please send the slides so I can share with everyone who participated at the meeting.

Thank you in advance.

Carissa

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Friday, April 03, 2015 4:27 PM
To: Cyran, Carissa
Subject: RE: Desk Statement

Carissa:

The Korean regulators (MFDS) will likely be sending you an email requesting EPA's view. Apparently they already sent one and haven't heard back.

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Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW

Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Cyran, Carissa [mailto:Cyran.Carissa@epa.gov]
Sent: Thursday, April 02, 2015 12:57 PM
To: LISTELLO, JENNIFER J [AG/1000]
Cc: JENKINS, DANIEL J [AG/1920]
Subject: RE: Desk Statement

Hello, Jen,

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Please let me know if you have any additional questions. Also, Dan, when you have the chance please send the redacted slides from the presentation on Monday.

Thank you,

Carissa

From: LISTELLO, JENNIFER J [AG/1000] [mailto:jennifer.j.listello@monsanto.com]
Sent: Thursday, April 02, 2015 12:23 PM
To: Cyran, Carissa
Cc: JENKINS, DANIEL J [AG/1920]
Subject: Desk Statement

Hi Carissa,

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I understand EPA has a desk statement regarding glyphosate/IARC. Can you please provide that statement?

Thanks,

Jen

To: 'LISTELLO, JENNIFER J [AG/1000]'[jennifer.j.listello@monsanto.com]
Cc: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]
From: Cyran, Carissa
Sent: Thur 4/2/2015 4:57:01 PM
Subject: RE: Desk Statement

Hello, Jen,

The EPA has issued the following desk statement regarding IARC and glyphosate.

In 1991 EPA concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) based on a lack of convincing carcinogenicity evidence and considering the criteria in EPA Guidelines for classifying a carcinogen. Since then, EPA has monitored emerging research on the carcinogenicity of glyphosate.

In 2014, EPA reviewed over 55 epidemiological studies conducted on the possible cancer and non-cancer effects of glyphosate. Our review concluded that this body of research does not provide evidence to show that glyphosate causes cancer, and it does not warrant any change in EPA's cancer classification for glyphosate. This is the same conclusion reached in 2004 by the United Nations' Food and Agriculture Organization and affirmed this year by Germany's pesticide regulatory officials. In a few months, EPA will be releasing for public comment our preliminary human health risk assessment for glyphosate as part of our program to reevaluate all pesticides periodically. EPA is aware of the recent International Agency for Research on Cancer (IARC) report and will address it in detail in the preliminary risk assessment. Additional information regarding glyphosate and EPA's ongoing registration review can be found at: http://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:31:0::NO:1,3,31,7,12,25:P3_XCHEMICAL_I

Please let me know if you have any additional questions. Also, Dan, when you have the chance please send the redacted slides from the presentation on Monday.

Thank you,

Carissa

From: LISTELLO, JENNIFER J [AG/1000] [mailto:jennifer.j.listello@monsanto.com]
Sent: Thursday, April 02, 2015 12:23 PM

To: Cyran, Carissa
Cc: JENKINS, DANIEL J [AG/1920]
Subject: Desk Statement

Hi Carissa,

Thanks for a great discussion on Monday; please let us know if there is anything additional that you need.

I understand EPA has a desk statement regarding glyphosate/IARC. Can you please provide that statement?

Thanks,

Jen

To: 'JENKINS, DANIEL J [AG/1920]'[daniel.j.jenkins@monsanto.com]
From: Cyran, Carissa
Sent: Tue 3/17/2015 5:09:07 PM
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Do you just want to meet with PRD or include other members from the team (BEAD, EFED)?

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, March 17, 2015 1:07 PM
To: Cyran, Carissa
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Hey Carissa do you think we could sit with you for 30 minutes prior to the meeting to talk about reg review generally? Would like to get an update and could share some things we're doing on monarchs

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Cyran, Carissa [mailto:Cyran.Carissa@epa.gov]
Sent: Tuesday, March 17, 2015 12:39 PM
To: JENKINS, DANIEL J [AG/1920]
Subject: FW: New proposed date and time for glyphosate breast milk discussion

Hi Dan,

I am confirming that the team is available on Monday, March 30 at 3:00-4:00.

Thank you,

Carissa

From: Cyran, Carissa
Sent: Monday, March 16, 2015 4:34 PM
To: 'JENKINS, DANIEL J [AG/1920]'
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Thank you Dan. I am waiting for one more confirmation and will confirm with you tomorrow.

Carissa

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Monday, March 16, 2015 1:05 PM
To: Cyran, Carissa
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Hey Carissa:

We'll take Monday at 3 pm ok?

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company

1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Cyran, Carissa [mailto:Cyran.Carissa@epa.gov]
Sent: Monday, March 16, 2015 12:25 PM
To: JENKINS, DANIEL J [AG/1920]
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Hello, Dan,

I wanted to follow up to see if any of the dates I proposed below work with your schedule. Thank you
Carissa

From: Cyran, Carissa
Sent: Monday, March 09, 2015 2:40 PM
To: 'JENKINS, DANIEL J [AG/1920]'
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Thank you Dan. Would you and your team be available on any of the following dates:

Monday, March 30th at 3:00

Tuesday, March 31st at 3:00

Thursday, April 2nd at 1:00 or 3:00

Thank you,

Carissa

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Thursday, March 05, 2015 8:46 AM
To: Cyran, Carissa
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Tues 10th or 17th or 19th work? We prefer afternoon so people can fly in and out the same day if possible.

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Cyran, Carissa [mailto:Cyran.Carissa@epa.gov]
Sent: Friday, February 27, 2015 12:58 PM
To: JENKINS, DANIEL J [AG/1920]
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Thanks Dan. Unfortunately we still do not have any information at this time we can share.

Carissa

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Friday, February 27, 2015 11:56 AM
To: Cyran, Carissa
Subject: RE: New proposed date and time for glyphosate breast milk discussion

Hey Carissa:

Looking at dates, will get back to you. do you think we can get a we could get a summary of EPA's method?

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: Cyran, Carissa [mailto:Cyran.Carissa@epa.gov]
Sent: Friday, February 27, 2015 10:48 AM
To: JENKINS, DANIEL J [AG/1920]
Subject: New proposed date and time for glyphosate breast milk discussion

Hello, Dan,

I apologize in advance, however, we need to reschedule the breast milk meeting that was scheduled for next Thursday. Could you please provide me with a few dates and times that work for your team?

Thank you,

Carissa

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To: Deener, Kathleen[Deener.Kathleen@epa.gov]
From: Burke, Thomas
Sent: Wed 5/4/2016 10:10:00 PM
Subject: Fwd: Letter to Administrator McCarthy
05.04.06 SST Letter to Administrator McCarthy re CARC.pdf
ATT00001.htm

Ex. 5 - Deliberative Process

Thomas A. Burke, PhD, MPH
Deputy Assistant Administrator
EPA Science Advisor
Office of Research and Development
202-564-6620
burke.thomas@epa.gov

Begin forwarded message:

From: "Distefano, Nichole" <DiStefano.Nichole@epa.gov>
Date: May 4, 2016 at 2:12:59 PM EDT
To: "Jones, Jim" <Jones.Jim@epa.gov>, "Burke, Thomas" <Burke.Thomas@epa.gov>
Cc: "Mitchell, Stacey" <Mitchell.Stacey@epa.gov>
Subject: FW: Letter to Administrator McCarthy

Ex. 5 - Deliberative Process

Nichole Distefano

Associate Administrator

Office of Congressional and Intergovernmental Relations

Environmental Protection Agency

(202) 564-5200

Distefano.Nichole@epa.gov

To: Jones, Jim[Jones.Jim@epa.gov]; Housenger, Jack[Housenger.Jack@epa.gov]; Keigwin, Richard[Keigwin.Richard@epa.gov]; Wise, Louise[Wise.Louise@epa.gov]; Mojica, Andrea[Mojica.andrea@epa.gov]
From: Strauss, Linda
Sent: Wed 5/4/2016 2:53:49 AM
Subject: Fwd: NYT FOIA Media FOIA concerning Glyphosate CARC

.....
,,,,,

Sent from my iPhone

Begin forwarded message:

From: "Conger, Nick" <Conger.Nick@epa.gov>
Date: May 3, 2016 at 6:47:08 PM EDT
To: "Milbourn, Cathy" <Milbourn.Cathy@epa.gov>, "Harrison, Melissa" <Harrison.Melissa@epa.gov>, "Hull, George" <Hull.George@epa.gov>, "Strauss, Linda" <Strauss.Linda@epa.gov>
Subject: RE: NYT FOIA Media FOIA concerning Glyphosate CARC

I think we need to make sure that this response does not go to the reporter until we have reviewed and are prepared from the comms end. Linda, can you ensure this does not move forward until we all are OK?

Sent from my Windows Phone

From: Milbourn, Cathy
Sent: 5/3/2016 6:21 PM
To: Harrison, Melissa; Conger, Nick; Hull, George
Subject: FW: NYT FOIA Media FOIA concerning Glyphosate CARC

Hi Melissa:

Please see the request below. This is just so you are aware.

Cathy

From: Ingram, Earl
Sent: Tuesday, May 03, 2016 6:12 PM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Keigwin, Richard <Keigwin.Richard@epa.gov>; Barber, Delores <barber.delores@epa.gov>; Hardy, Michael <Hardy.Michael@epa.gov>; Goodis, Michael

<Goodis.Michael@epa.gov>; Nguyen, Khue <Nguyen.Khue@epa.gov>; Rowland, Jess <Rowland.Jess@epa.gov>; Smith, Charles <Smith.Charles@epa.gov>; Middleton, Karlyn <Middleton.Karlyn@epa.gov>; Koch, Erin <Koch.Erin@epa.gov>
Subject: Media FOIA concerning Glyphosate CARC

Everyone,

Today, OPP received a FOIA from Danny Hakim, reporter from the New York Times, for information on the Glyphosate CARC (description below and request attached). Janet Bressant will be our lead on this FOIA request. She has worked with PRD staff in recent months on a number glyphosate requests.

The request is limited in scope and time. Since the request is asking only for emails, we will submit a request to the E-Discovery Team to search the emails for the listed individuals. We will review the records for any information exempted from release under FOIA. We will work with Erin, prior to releasing any records.

I request e-mail traffic related to "glyphosate" and/or the glyphosate review process to/from the following people: Jess Rowland and Karlyn Middleton, the chair and co-chair of the Cancer Assessment Review Committee, as well as Charles Smith (Chief, Risk Assessment Branch I, Health Effects Division), and Khue Nguyen, chemical review manager. The time period covered should be May 1, 2015 through today.

Feel free to contact Janet or myself if you have any questions.

Earl Ingram, Chief

Public Information & Records Integrity Branch

Information Technology & Resources Management Division

Office of Pesticide Programs

U.S. Environmental Protection Agency

(703) 305-5456

Cc: Mojica, Andrea[Mojica.andrea@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]
To: Housenger, Jack[Housenger.Jack@epa.gov]; Keigwin, Richard[Keigwin.Richard@epa.gov]
From: Jones, Jim
Sent: Wed 5/4/2016 11:42:34 AM
Subject: Fwd: glyphosate: POLITICO on EPA report

Ex. 5 - Deliberative Process

Sent from my iPhone

Begin forwarded message:

From: Chris Portier **Ex. 6 - Personal Privacy**
Date: May 4, 2016 at 7:38:18 AM EDT
To: Jim Jones <Jones.jim@Epa.gov>
Subject: Fwd: glyphosate: POLITICO on EPA report

Jim,
FYI.

C.

Subject: glyphosate: POLITICO on EPA report

GLYPHOSATE STORM'S A-BREWIN': The U.S. Environmental Protection Agency has made a preliminary finding that glyphosate is unlikely to cause cancer in humans — but the agency isn't ready to go public yet. The EPA briefly posted online an October 2015 final report from its Cancer Assessment Review Committee, which concluded glyphosate is "not likely to be carcinogenic to humans." It then pulled it from its website. The committee said evidence from existing epidemiological studies and tests of lab animals doesn't meet the bar for classifying the herbicide as a carcinogen. An agency spokesperson told POLITICO the report was removed because assessment was ongoing. "Our assessment will be peer reviewed and completed by end of 2016," said the spokesperson.

— Why this matters for the EU: A political scrum over what to do about glyphosate is underway in the EU. Parliament voted to extend the

chemical's authorization for seven years, the Commission is pushing for 10, but the real decision comes in a Plant, Animal, Food and Feed Committee meeting on May 18-19. Advocates for banning glyphosate altogether cite a March 2015 study by International Agency for Research on Cancer, which said it caused cancer. Glyphosate's political supporters cite a November study with the opposite conclusions. This latter group might now have another study in their arsenal — and from a reputable U.S. government agency. "In line with the 90,000 pages, and 3,300 studies already published in support of the reapproval of glyphosate, the EPA report casts yet more doubt on the conclusions of IARC," a spokesperson for the European Crop Protection Association told Morning Agri. Greenpeace EU, which opposes using glyphosate as long as there is no scientific consensus, told Morning Agri it had not yet read the study and so couldn't comment. More: http://reut.rs/23mbxYf.

To: Burke, Thomas[Burke.Thomas@epa.gov]
Cc: Distefano, Nichole[DiStefano.Nichole@epa.gov]; Mitchell, Stacey[Mitchell.Stacey@epa.gov]
From: Jones, Jim
Sent: Thur 5/5/2016 12:42:19 AM
Subject: Re: Letter to Administrator McCarthy

Ex. 5 - Deliberative Process

Sent from my iPhone

On May 4, 2016, at 6:12 PM, Burke, Thomas <Burke.Thomas@epa.gov> wrote:

Will get back with an answer ASAP.

Thomas A. Burke, PhD, MPH
Deputy Assistant Administrator
EPA Science Advisor
Office of Research and Development
202-564-6620
burke.thomas@epa.gov

On May 4, 2016, at 2:13 PM, Distefano, Nichole <DiStefano.Nichole@epa.gov> wrote:

Ex. 5 - Deliberative Process

Nichole Distefano

Associate Administrator

Office of Congressional and Intergovernmental Relations

Environmental Protection Agency

(202) 564-5200

Distefano.Nichole@epa.gov

<05.04.06 SST Letter to Administrator McCarthy re CARC.pdf>

To: Middleton, Karlyn[Middleton.Karlyn@epa.gov]
From: Rowland, Jess
Sent: Fri 9/18/2015 2:01:39 PM
Subject: RE: edits

Ex. 6 - Personal Privacy

Sent from my Windows Phone

From: Middleton, Karlyn
Sent: 9/18/2015 9:57 AM
To: Rowland, Jess
Subject: RE: edits

Is this the right number?

From: Rowland, Jess
Sent: Friday, September 18, 2015 9:02 AM
To: Middleton, Karlyn
Subject: edits

Hi

My edits in blue. After u r input, let us send it to PRD….not to Monique!!

Also can u call me at Ex. 6 - Personal Privacy I need to consult on the final report….

1. The International Agency on the Research for Cancer (IARC) released their final conclusions that glyphosate is likely to cause cancer. What is EPA's position on this and how is this information being considered?

Ex. 5 - Deliberative Process

2. Why does EPA disagree with the IARC assessment? How can EPA and IARC come to different conclusions about glyphosate's ability to cause cancer?

Ex. 5 - Deliberative Process

3. Is it true that glyphosate is linked to Parkinson's disease and Non-Hodgkin's Lymphoma?

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Middleton, Karlyn[Middleton.Karlyn@epa.gov]
From: Vogel, Dana
Sent: Wed 9/9/2015 3:15:32 PM
Subject: Re: pls add anna to glyphosate carc meeting

U rule!

Dana Vogel
Sent from my iPhone

On Sep 9, 2015, at 11:01 AM, Middleton, Karlyn <Middleton.Karlyn@epa.gov> wrote:

I sent her the invitation yesterday.

From: Vogel, Dana
Sent: Wednesday, September 09, 2015 11:01 AM
To: Middleton, Karlyn
Subject: pls add anna to glyphosate carc meeting

Thanks!!

Director, Health Effects Division

Office of Pesticide Programs

USEPA

To: Rowland, Jess[Rowland.Jess@epa.gov]; Schlosser, Christopher[Schlosser.Christopher@epa.gov]; Middleton, Karlyn[Middleton.Karlyn@epa.gov]; Swartz, Christina[Swartz.Christina@epa.gov]; Davis, Donna[Davis.Donna@epa.gov]; Morton, Thurston[Morton.Thurston@epa.gov]
Cc: Kidwell, Jessica[kidwell.jessica@epa.gov]
From: Kidwell, Jessica L
Sent: Wed 9/9/2015 1:55:07 PM
Subject: RE: Carc

Trust me, you want Jessica M. instead of Jessica L. on this one. I've copied her here.

Thanks, Jessica L.

From: Rowland, Jess
Sent: Wednesday, September 09, 2015 8:52 AM
To: Schlosser, Christopher; Kidwell, Jessica L; Middleton, Karlyn; Swartz, Christina; Davis, Donna; Morton, Thurston
Subject: Carc

Chris
I have asked Jessica to be Ex.Sec for the Glyphosate CARC.
JR

Sent from my Windows Phone

To: Middleton, Karlyn[Middleton.Karlyn@epa.gov]
From: Miller, David
Sent: Tue 5/26/2015 1:42:48 PM
Subject: Automatic reply: Glyphosate CARC Meeting

I will be out of the office on annual leave beginning 22 May and returning on Monday 01 June. I will have at least sporadic access to email during this time

If you need assistance during this time, please contact Matthew Crowley who will be acting branch chief at crowley.matthew@epa.gov

To: Kidwell, Jessica[kidwell.jessica@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]
From: Middleton, Karlyn
Sent: Wed 9/23/2015 3:36:12 PM
Subject: RE: Glyphosate CARC tReport

I think that would be good. Otherwise, we will have a lot of different versions.

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 11:30 AM
To: Middleton, Karlyn; Rowland, Jess
Cc: Brunsman, Lori; Dunbar, Anwar; Liccione, John; McCarroll, Nancy; Chen, Jonathan; Kent, Ray; Schlosser, Christopher; Akerman, Gregory
Subject: RE: Glyphosate CARC tReport

Yes, Greg and I can't either. I'm actually using Cal's version since he made formatting edits instead of the file on the share drive that Lori's referring to. Do you want me to share this file?

From: Middleton, Karlyn
Sent: Wednesday, September 23, 2015 11:27 AM
To: Rowland, Jess
Cc: Brunsman, Lori; Dunbar, Anwar; Kidwell, Jessica; Liccione, John; McCarroll, Nancy; Chen, Jonathan; Kent, Ray; Schlosser, Christopher; Akerman, Gregory
Subject: RE: Glyphosate CARC Report

Hi all,

For some reason, I can't upload my comments to share point. It says that its locked for editing for me. Did this happen to anyone else?

From: Rowland, Jess

Sent: Tuesday, September 22, 2015 2:01 PM
To: Akerman, Gregory; Brunsman, Lori; Dunbar, Anwar; Kidwell, Jessica; Liccione, John; Middleton, Karlyn; McCarroll, Nancy; Chen, Jonathan; Kent, Ray; Schlosser, Christopher
Subject: Glyphosate CARC Report

Hi

Hope you all received the CARC draft thru sharepoint.

Please make the edits on sharepoint so I can see the comments

Do NOT waste time on format, paginations, tabs etc. CPR is do the "document makeover"

Concentrate on the science

Make this as your priority and your "home pope work" on Wednesday

I would like to have your comments not later than COB Thursday

Thank you for all your work on this CARC

Regards

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Middleton, Karlyn
Sent: Tue 9/22/2015 6:06:33 PM
Subject: RE: Glyphosate CARC Report

Will do.

From: Rowland, Jess
Sent: Tuesday, September 22, 2015 2:01 PM
To: Akerman, Gregory; Brunsman, Lori; Dunbar, Anwar; Kidwell, Jessica; Liccione, John; Middleton, Karlyn; McCarroll, Nancy; Chen, Jonathan; Kent, Ray; Schlosser, Christopher
Subject: Glyphosate CARC Report

Hi

Hope you all received the CARC draft thru sharepoint.

Please make the edits on sharepoint so I can see the comments

Do NOT waste time on format, paginations, tabs etc. CPR is do the "document makeover"

Concentrate on the science

Make this as your priority and your "home pope work" on Wednesday

I would like to have your comments not later than COB Thursday

Thank you for all your work on this CARC

Regards

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Middleton, Karlyn
Sent: Fri 9/18/2015 2:05:49 PM
Subject: RE: edits

That's not working either….call me at Ex. 6 - Personal Privacy

From: Rowland, Jess
Sent: Friday, September 18, 2015 10:02 AM
To: Middleton, Karlyn
Subject: RE: edits

Ex. 6 - Personal Privacy

Sent from my Windows Phone

From: Middleton, Karlyn
Sent: 9/18/2015 9:57 AM
To: Rowland, Jess
Subject: RE: edits

Is this the right number?

From: Rowland, Jess
Sent: Friday, September 18, 2015 9:02 AM
To: Middleton, Karlyn
Subject: edits

Hi

My edits in blue. After u r input, let us send it to PRD….not to Monique!!

Also can u call me at Ex. 6 - Personal Privacy I need to consult on the final report….

1. The International Agency on the Research for Cancer (IARC) released their final conclusions that glyphosate is likely to cause cancer. What is EPA's position on this and how is this information being considered?

Ex. 5 - Deliberative Process

2. Why does EPA disagree with the IARC assessment? How can EPA and IARC come to different conclusions about glyphosate's ability to cause cancer?

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

3. Is it true that glyphosate is linked to Parkinson's disease and Non-Hodgkin's Lymphoma?

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Middleton, Karlyn
Sent: Fri 9/18/2015 1:57:50 PM
Subject: RE: edits

Is this the right number?

From: Rowland, Jess
Sent: Friday, September 18, 2015 9:02 AM
To: Middleton, Karlyn
Subject: edits

Hi

My edits in blue. After u r input, let us send it to PRD….not to Monique!!

Also can u call me at Ex. 6 - Personal Privacy I need to consult on the final report….

1. The International Agency on the Research for Cancer (IARC) released their final conclusions that glyphosate is likely to cause cancer. What is EPA's position on this and how is this information being considered?

Ex. 5 - Deliberative Process

2. Why does EPA disagree with the IARC assessment? How can EPA and IARC come to different conclusions about glyphosate's ability to cause cancer?

Ex. 5 - Deliberative Process

3. Is it true that glyphosate is linked to Parkinson's disease and Non-Hodgkin's Lymphoma?

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Swartz, Christina[Swartz.Christina@epa.gov]
From: Middleton, Karlyn
Sent: Thur 9/10/2015 4:41:06 PM
Subject: RE: flexiplace AM; Leave PM

Did you get a chance to look at the HASPOC memo yet? I'll be working until 1:30 pm today. However, I'll check my email periodically for it… thanks!

From: Swartz, Christina
Sent: Thursday, September 10, 2015 8:15 AM
To: Middleton, Karlyn
Subject: RE: flexiplace AM; Leave PM

Okay – **Ex. 6 - Personal Privacy**

C

From: Middleton, Karlyn
Sent: Thursday, September 10, 2015 6:32 AM
To: Swartz, Christina
Subject: flexiplace AM; Leave PM

Hi Christina,

Ex. 6 - Personal Privacy

Ex. 6 - Personal Privacy I have a glyphosate CARC pre meeting at 8am that I plan to attend. I will also review the glyphosate CARC document, finish up diuron so I can send it to Jess and Dana, and incorporate team comments into my HASPOC memo to forward to you. I'll be checking my email so you can send me the HASPOC memo when you are done. I'll incorporate your comments and forward it to Uma. Thanks.

To: Swartz, Christina[Swartz.Christina@epa.gov]
From: Middleton, Karlyn
Sent: Thur 9/10/2015 2:29:19 PM
Subject: diphenylamine HASPOC memo
diphenylamine HASPOC_9-10-15.docx

See diphenylamine HASPOC memo attached.

From: Swartz, Christina
Sent: Thursday, September 10, 2015 8:15 AM
To: Middleton, Karlyn
Subject: RE: flexiplace AM; Leave PM

Okay – Ex. 6 - Personal Privacy

C

From: Middleton, Karlyn
Sent: Thursday, September 10, 2015 6:32 AM
To: Swartz, Christina
Subject: flexiplace AM; Leave PM

Hi Christina,

Ex. 6 - Personal Privacy

Ex. 6 - Personal Privacy I have a glyphosate CARC pre meeting at 8am that I plan to attend. I will also review the glyphosate CARC document, finish up diuron so I can send it to Jess and Dana, and incorporate team comments into my HASPOC memo to forward to you. I'll be checking my email so you can send me the HASPOC memo when you are done. I'll incorporate your comments and forward it to Uma. Thanks.

To: Swartz, Christina[Swartz.Christina@epa.gov]
From: Middleton, Karlyn
Sent: Thur 9/10/2015 10:32:03 AM
Subject: flexiplace AM; Leave PM

Hi Christina,

Ex. 6 - Personal Privacy

Ex. 6 - Personal Privacy I have a glyphosate CARC pre meeting at 8am that I plan to attend. I will also review the glyphosate CARC document, finish up diuron so I can send it to Jess and Dana, and incorporate team comments into my HASPOC memo to forward to you. I'll be checking my email so you can send me the HASPOC memo when you are done. I'll incorporate your comments and forward it to Uma. Thanks.

To: Vogel, Dana[Vogel.Dana@epa.gov]
From: Middleton, Karlyn
Sent: Wed 9/9/2015 3:01:29 PM
Subject: RE: pls add anna to glyphosate carc meeting

I sent her the invitation yesterday.

From: Vogel, Dana
Sent: Wednesday, September 09, 2015 11:01 AM
To: Middleton, Karlyn
Subject: pls add anna to glyphosate carc meeting

Thanks!!

Director, Health Effects Division

Office of Pesticide Programs

USEPA

From: Middleton, Karlyn
Location: 10621
Importance: Normal
Subject: FW: Glyphosate - CARC - Continues.....
Start Date/Time: Wed 9/16/2015 5:00:00 PM
End Date/Time: Wed 9/16/2015 8:00:00 PM

-----Original Appointment-----
From: Rowland, Jess
Sent: Thursday, July 30, 2015 9:16 AM
To: Rowland, Jess; Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kidwell, Jessica; Liccione, John; Middleton, Karlyn; McCarroll, Nancy; Shah, Pv; Kent, Ray; Lobdell, Danelle; Woo, Yintak; Wood, Charles; Morton, Thurston
Subject: Glyphosate - CARC - Continues.....
When: Wednesday, September 16, 2015 1:00 PM-4:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: 10621

Given the volume of data we have to review, I have scheduled this PM session.
This CARC should be a priority for you. So keep this day OPEN
Please adjust your other commitments for the day

From: Middleton, Karlyn
Location: 10100
Importance: Normal
Subject: FW: Glyphosate - CARC
Start Date/Time: Wed 9/16/2015 1:00:00 PM
End Date/Time: Wed 9/16/2015 4:00:00 PM

-----Original Appointment-----
From: Rowland, Jess
Sent: Monday, July 27, 2015 2:21 PM
To: Rowland, Jess; Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Kent, Ray; Kidwell, Jessica; Liccione, John; Lobdell, Danelle; Middleton, Karlyn; Shah, Pv; Woo, Yintak; Wood, Charles; Morton, Thurston; Smith, Charles; McCarroll, Nancy; Dunbar, Anwar
Subject: Glyphosate - CARC
When: Wednesday, September 16, 2015 9:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: 10100

Greg et al.,

Please note the earlier start time
Make necessary changes to your schedule to accommodate this meeting.
You will receive the CARC package on September 2nd.
Thanks

JR

From: Middleton, Karlyn
Location: S-10621
Importance: Normal
Subject: Accepted: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 1:00:00 PM
End Date/Time: Thur 9/10/2015 2:00:00 PM

From: Middleton, Karlyn
Location: S-10621
Importance: Normal
Subject: New Time Proposed: CARC pre=meet for glyphosate
Start Date/Time: Thur 9/10/2015 1:00:00 PM
End Date/Time: Thur 9/10/2015 2:00:00 PM

To: Smith, Charles[Smith.Charles@epa.gov]
Cc: Rowland, Jess[Rowland.Jess@epa.gov]
From: Middleton, Karlyn
Sent: Thur 8/13/2015 7:12:57 PM
Subject: CARC FY 15 Accomplishments

FYI…

From: Brunsman, Lori
Sent: Thursday, August 13, 2015 7:13 AM
To: Middleton, Karlyn
Subject: RE: FY 15 Accomplishments

Sure!

In FY15:

CARC: 4 peer review meetings on 4 chemicals for cancer classification by the CARC (the last of these 4 meetings is Glyphosate on 9/16/15)

Have a great day!

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov

703-308-2902

From: Middleton, Karlyn
Sent: Wednesday, August 12, 2015 3:46 PM
To: Brunsman, Lori
Cc: Rowland, Jess
Subject: FW: FY 15 Accomplishments

Hi Lori,

Can you pull this together for the CARC meetings last fiscal year? See last year highlighted. Thank you!

From: Smith, Charles
Sent: Tuesday, August 11, 2015 12:52 PM
To: Olinger, Christine; Dawson, Jeffrey; Shelat, Shalu; Rury, Kristin; Perron, Monique; Middleton, Karlyn; Reaves, Elissa; Mendez, Elizabeth; Davis, Donna; Wilbur, Donald; VanAlstine, Julie; Morton, Thurston; Piper, Sheila; Kidwell, Jessica; Dunbar, Anwar; Lowit, Anna; Britton, Wade; Lowe, Kelly
Cc: Vogel, Dana; Rowland, Jess
Subject: FY 15 Accomplishments

All,

The HED management team is working on HED's FY 15 accomplishments. As part of that work, we are trying to put together a list of the SAC/SARC meetings that have occurred throughout the year. I have copied below what we put into last year's accomplishments document. I am hoping that those involved with each SAC/SARC can provide some similar brief write-up for FY 15. I need this done by no later than noon next Monday (8/17). If you have any questions, please feel free to let me know. Thanks!

SAC/SARC Meetings:

• ExpoSAC: 30 peer review meetings on various technical issues as well as for review of occupational and residential exposure assessments produced in support of risk assessment. State pesticide representatives were invited to 6 of these meetings and ExpoSAC members had open discussions with these representatives about various occupational and residential exposure issues they were dealing with in their individual states.

• ToxSAC: 31 peer review meetings for endpoint selection or protocol reviews in support of risk assessment. Including 4 new active ingredients (Halauxifen-methyl, Bicyclopyrone, Solatenol, Momfluorthrin), 7 OPs (Acephate, Pirimiphos-methyl, Malathion, Terbufos, Chlorethoxyfos, Diazinon, Ethoprop), which updated BMD modeling and steady state assessments for Registration Review, as well as other chemicals in support of Registration Review.

• ChemSAC: 21 Meetings on various issues as well as technical review of residue chemistry documents. Development of science policy on processed commodities. Provide training to branch chemists. Included PMRA and IR-4 in multiple meetings.

• DESAC: 15 meetings on various issues along with detailed review of probabilistic dietary assessments (Dicrotophos, Thiabendazole, Prallethrin, Chlorpyrifos, Deltamethrin, etc.) and training of the new RDF generator program, USDA PDP Monitoring Program, and manual creation of RDFs for use in acute probabilistic assessments. In addition, there were 3 training sessions on the use of Calendex for steady state dietary assessments, a Commodity Specific Analysis refresher training, and a discussion about the new DEEM User Guide. The SAC also met twice to discuss the processing factors table that was developed by the ChemSAC Processing Factors Focus Group and provided feedback on the "Summary of EPA's Uncertainty and Variability Data Call Responses" document.

• ROCKS: 8 meetings (Flupyradifurone; Halauxifen-methyl; Benzovindiflupyr; Terbufos; Tricyclazole (e-review); Isofetamid; Benalaxyl-M; Bicyclopyrone). Several Co-chair consultations

• CARC: 10 peer review meetings on 11 chemicals for cancer classification by the CARC

• DART: 4 DART meetings related to dose selection for rat and/or mouse carcinogenicity and immunotoxicity studies

• HASPOC: HASPOC reviewed data waivers for 86 chemicals for a variety of toxicity studies, primarily for the acute and subchronic neurotoxicity, subchronic inhalation studies, and immunotoxicity studies. Waivers were granted for 51 of the 57 requests for a subchronic inhalation studies resulting in the savings of approximately 4000 animals and $4 million, the cost of conducting these studies. Similarly, waivers were granted for 31 of the 35 requests for the neurotoxicity studies, resulting the saving of approximately 5000 animals and $5 million, the cost of conducting these studies. Finally, waivers were granted for 46 of the 49 requests for immunotoxicity studies, resulting the saving of approximately 750 animals and $3 million, the cost of conducting these studies.

•□□□□□□ RARC: The RARC reviewed 15 risk assessments: 4 new active ingredients (tricyclazole; fluensulfone; halauxifen-methyl; isofetamid); 1 first food use (flupyradifurone); 6 Registration Review Risk Assessments (hydrogen cyanamide; cyromazine; dicrotophos; clethodim; chlorfenapyr; tebuthiuron;); 1 pre-RARC meeting (flupyradifurone);1 e-review (flutolanil); and 2 other assessments (Prallethrin (label amendment for mosquitocide use); deltamethrin (tolerance without US registration for use on finfish).

Charles " Billy" Smith

Branch Chief RAB4

Health Effects Division

Office of Pesticide Programs

703-305-0291

From: Middleton, Karlyn
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate - CARC - Continues.....
Start Date/Time: Wed 9/16/2015 5:00:00 PM
End Date/Time: Wed 9/16/2015 8:00:00 PM

From: Middleton, Karlyn
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate CARC - Preparation
Start Date/Time: Thur 7/30/2015 3:00:00 PM
End Date/Time: Thur 7/30/2015 4:00:00 PM

From: Middleton, Karlyn
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate CARC - Preparation
Start Date/Time: Wed 7/29/2015 2:00:00 PM
End Date/Time: Wed 7/29/2015 3:00:00 PM

From: Middleton, Karlyn
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate CARC - Preparation
Start Date/Time: Wed 7/29/2015 1:00:00 PM
End Date/Time: Wed 7/29/2015 2:00:00 PM

From: Middleton, Karlyn
Location: 10100
Importance: Normal
Subject: Accepted: Glyphosate - CARC
Start Date/Time: Wed 9/16/2015 1:00:00 PM
End Date/Time: Wed 9/16/2015 4:00:00 PM